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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

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Terry Munson
Russ Madsen

FDA Speakers

Richard Friedman
David Hussong
Kris Evans
Robert Sausville
Brenda Uratani, Ph.D.

FDA

Douglas I. Ellsworth
Jay Elterman
Joseph Famulare
Ajaz Hussain, Ph.D.
Helen Winkle

at

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P R O C E E D I N G S

Call to Order

DR. LEE: Good morning. I am Victor Lee, Department of Pharmaceutical Sciences, School of Pharmacy at the University of Southern California in Los Angeles. I am the Chair of this Committee, the Committee for Pharmaceutical Science.

Let me begin by asking the folks around the table to introduce themselves. Ajaz?

DR. HUSSAIN: Ajaz Hussain, Deputy Direction, Office of Pharmaceutical Science.

DR. MOYE: University of Texas, Biostatistics.

DR. JUSKO: William Jusko, University of Buffalo.

DR. MEYER: Marvin Meyer, Emeritus Professor, University of Tennessee.

DR. KIBBE: Art Kibbe, Professor, Wilkes University.

DR. ANDERSON: Gloria Anderson, Callaway Professor of Chemistry, Morris Brown College.

DR. BLOOM: Joseph Bloom, University of Puerto Rico.

DR. BOEHLERT: Judy Boehlert. I have my own pharmaceutical business.

DR. SHARGEL: Leon Shargel, Eon Laboratories.

DR. SHEK: Efraim Shek, Abbott Laboratories.

MR. MIGLIACCIO: Gerry Migliaccio, Vice President of Global Operations from Pfizer representing PhRMA.

MR. LAVIN: Ken Lavin, Director of Regulatory Compliance with Teva Pharmaceuticals representing GphA.

DR. LEE: Thank you very much. Kathleen, are you ready? We are kind of short-handed this morning. Kathleen is going to read us the conflict-of-interest statement.

Conflict of Interest

MS. REEDY: The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The topics of today's meeting are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industry sponsors and academic institutions.

All special government employees and federal guests have been screened for their financial interests as they may apply to the general topics at hand. Because they have reported interests in pharmaceutical companies, the Food and Drug Administration has granted waivers to the following special government employees which permits them to participate in today's discussions: William J. Jusko, Ph.D and Judy Boehlert, Ph.D.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A30 of the Parklawn Building

Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest as they apply to each member, consultant and guest. FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the committee, these potential conflicts are mitigated.

We would like to note for the record that Dr. Efraim Shek of Abbott Laboratories and Dr. Leon Shargel of Eon Labs are participating in this meeting as industry representatives acting on

behalf of regulated industry. As such, they have not been screened for any conflicts of interest.

DR. LEE: Thank you, Kathleen.

I would like to begin the meeting by inviting Dr. Ajaz Hussain, Deputy Director of the OPS to give us the charge.

Future Subcommittee--GMP/Manufacturing

Introduction and Overview

DR. HUSSAIN: Good morning.

[Slide.]

I have prepared the presentation to talk about the Manufacturing Subcommittee that we proposed at a previous meeting and sort of lay out some details on that.

I also have a backup set of slides that I thought I could use to spend a bit more time to give all of our other FDA colleagues to get together because of the incident this morning. So I think I can spend some time explaining this in a bit more detail than I had originally planned.

[Slide.]

At a previous meeting, we had proposed to you that we would like to create a subcommittee on pharmaceutical manufacturing and that the PAT subcommittee would essentially sunset as this

complication sort of comes to become functioning.

Just to give you a sense, manufacturing, pharmaceutical manufacturing, is addressed by different parts of the Agency as it is done differently in companies, too. So we essentially are looking at the quality system which includes how do we set specifications to the test and controls and falling GMPs and then, also including, from a quality perspective, making sure the specifications make sense, are linked to safety and efficacy and then, when there are changes, how do you manage to insure that the product performance is unchanged.

So the quality system is quite a complex system with different parts of the Agency including a public standard-setting organization--that is, USP--that sort of comes to play in the overall quality system. So, if you start looking at it, how does each and every component work and how are these interlinked, I think it is time to take a hard look on that and see what improvements in the scientific foundation of this system can be done.

[Slide.]

So from the background perspective, pharmaceutical manufacturing is a very critical

component of the industry and it has to function as efficiently as it can to make sure the quality products are available to the U.S. public.

Manufacturing depends on R&D in developing optimal dosage forms. So I think the review part which we deal with, mostly R&D, has to set the specifications that are appropriate from a safety and efficacy perspective but also the specifications should be such that the manufacturability is considered appropriately.

So you are looking at R&D and manufacturing as two big clumps within the industry and sort of, in reflection to that, you have the review and inspective clumps, and how do these function, I think, is an important goal of understanding this so that we can do a more efficient job.

We started the PAT initiative about a year ago and that was with this in mind, how do you approve the science. That essentially has led to the new FDA initiative on cGMP for the 21st Century. So you have two major initiatives that are addressing pharmaceutical manufacturing in a global sense.

[Slide.]

The need for the Manufacturing Subcommittee was apparent to us even before we started the cGMP for the 21st Century initiative. So this Manufacturing Subcommittee we are proposing is to provide input and advice to CDER and FDA so manufacturing is not just Center for Drugs Review and Compliance, it is Office of Regulatory Affairs, and so forth. So this committee will have a much broader focus and input to the entire FDA in many senses.

Our original plan was to use this Manufacturing Subcommittee to bring input to FDA on science-based CMC and GMP policies. But, keeping in mind the broader scope, and the sunset of the PAT Subcommittee, we would also like this committee to focus on providing input to us on continued development of the PAT initiative.

Keep in mind, the PAT initiative with the subcommittee leads to a general guidance, but there will be need for many technical guidances that will have to be developed in this area and we will look to this committee for input on those issues.

Clearly, the cGMP for the 21st Century, a risk-based approach, will benefit from a lot of the discussions that can occur at this subcommittee.

So that is the thought process as to the scope of the subcommittee. It would range from very focused discussion on some topics. One example is the aseptic manufacturing discussion we have this afternoon to a broader discussion on other issues, too.

[Slide.]

We plan to model the Manufacturing Subcommittee after the PAT Subcommittee. It think the PAT Subcommittee was, in my mind, a very successful subcommittee that, with three meetings, gathered all the expertise and brought information to the FDA to help us write the draft guidance. Tomorrow is the last meeting, in once sense, of the PAT Subcommittee.

What we have learned from that is if you identify the right individuals who have the scientific expertise, it really helps to sort of crystalize the process very well.

Based on that sort of experience, what we are proposing is we will have a set of core membership, which is based on expertise in manufacturing and quality assurance to be part of this subcommittee. Some members of the PAT Subcommittee will be invited to participate as the

PAT Subcommittee sunset, so you will have continuity built in.

Then, once we have the core membership, we will have focused working groups or fact-finding groups which will sunset their activities after they have done their job. So this will be fluid working groups and fact-finding groups which will be assigned the task. Once they have completed it, they will sunset their activities and the entire group will focus on other areas.

Since the cGMP for the 21st Century has many immediate steps outlined, initial topics that we may need to focus on under the subcommittee may be some selected immediate steps outlined in the cGMP for the 21st Century Concept Paper. That is one of the possibilities.

[Slide.]

Here what I thought I would do is take a step backward and sort of look at the 21st Century Concept Paper that we have distributed to you and share some more information about this initiative. There were many drivers that led to this initiative and what we have seen over the last two decades is increased numbers of pharmaceuticals and their greater role in healthcare. In fact, several years

ago, the cost of drugs exceeded the cost of hospital care. So, the importance of medicines or drugs in healthcare is tremendous. At the same time, over the last decade, we have seen a decreased frequency of inspections. There are many reasons for that.

Also, we have been accumulating our experience in lessons learned from various approaches to product quality but we have been doing that in segments. It is now time to take a step back and sort of look at the entire system and make sure the connections are there.

Clearly, there have been advances in pharmaceutical scientific and manufacturing technology. Although we have brought some of these in on a step-by-step basis, it is again time to sort of look back and see how do we bring all of this into a complete system.

Application of biotechnology not only for drug discovery but also for drug development and for manufacturing--there are a lot of lessons to be learned from that. Clearly, there have been advancements in science and management of quality, itself. That revolution, the quality revolution, I think we can learn a lot from that. Clearly, we

are looking at a global industry rather than just the U.S. industry, itself.

[Slide.]

The pharmaceutical cGMP for the 21st Century essentially describes that initiative as a science- and risk-based approach to product-quality regulation incorporating an integrated quality-systems approach. That is sort of the basic foundation of this initiative. It is intended to incorporate a more up-to-date concept of risk management and scientific advances, encourage innovation and continuous improvement, ensure that submission review and cGMP inspection are coordinated and are synergistic and also ensure we have consistency and effective utilization of our resources.

So, in many ways, when you look at the title, the title is a bit narrow and I think the scope of this--in my mind, the correct title would be a drug-quality system for the 21st Century instead of cGMP. It is an entire system that we are looking at.

[Slide.]

The guiding principles that we have developed for this initiative are several. We will

have a risk-based orientation, science-based policies and standards, integrated quality-system orientation, international cooperation. Clearly, the strong public-health protection is always the foundation on which we will base all this on.

[Slide.]

We have outlined several steps. We are in the process of performing an external review of our existing cGMP programs and product-review practices including evaluation of potential inconsistencies in the implementation, reassess and revaluate our scientific approach to both the product-review process and cGMP program to achieve a consistent integrated-systems approach to product-quality regulation, enhance the scientific approach of cGMPs to emphasize risk-based control-point analysis and to facilitate the latest innovation in pharmaceutical engineering.

Those are the sort of broad steps that we have outlined.

[Slide.]

We have set for ourselves some immediate steps. An immediate step means we would have some results within six months. February is the deadline we are looking at. It doesn't mean we

will implement all that. We will have developed our understanding and our plans to a degree that we can actually start presenting some of these immediate steps to the stakeholders.

Among the immediate steps which I think will be the focus of some of our discussions in the subcommittee, holding scientific workshops with key stakeholders, enhancing expertise in pharmaceutical technology; for example, pharmaceutical engineering and industrial pharmacy by additional training and hiring and by leveraging external expertise, encouraging innovation within the existing framework by allowing certain changes in manufacturing processes without prior review or approval; for example, use of comparability protocols.

So I believe those are the main topics that we might start out in the subcommittee.

[Slide.]

But, there are other steps which may not be directly linked to the subcommittee activities which may include evaluating the optimal mechanism for effectively and efficiently communicating deficiencies to industry including content, consistency, disclosure and education; shifting the

Agency lead on implementation of Part 11 to CDER--that has already occurred--with continued involvement from other centers in ORA; including product specialists as needed as part of the inspection team

[Slide.]

Having centers provide a scientific and technical review of all drug cGMP warning letters; developing a technical dispute-resolution process that integrates technical experts from the Centers and addresses perceived inconsistencies between Centers; emphasizing a risk-based approach in the work-planning process and improving the operation of Team Biologics.

[Slide.]

The way we are moving forward is we essentially have created a set of working groups and a GMP Steering Committee. This is just to show the number of working groups active that are focused on the initial short-term milestone which is six months or less. We have a group on Contract Management, International Activities, Part 11, Dispute Resolution, Warning Letter Review, 483 Communications, Changes without Prior Review, Product Specialists on Inspection Team, Working

Planning and Risk Management, Cadre of Investigators, Developing Science Aspect, Evaluation of the Initiative, itself, and Quality Systems.

We have not started working on a Training Program at this time.

[Slide.]

SO, with that sort of a backdrop, I just wanted to share some thoughts on what the Manufacturing Subcommittee might take up as initial topics. Potential discussion topics, as examples, could include, I think, starting with Definitions and Common Understanding. What do we mean by a risk-based approach in the context of manufacturing. I think we would need to start discussing and sort of building a common consensus on what does risk constitute or in the context of manufacturing, what does that mean?

What do we mean by an integrated-systems approach? What is meant by a science-based approach? We have always been a science-based agency but what is different now? Science of quality? What is that and what is modern quality thinking, and so forth?

So these are some examples of the words we

use but which may have different meaning to different individuals and we need to have some common understanding.

[Slide.]

Just to give you sort of my way of looking at some of these words, if I go to Webster and pick up the definitions which I think apply. First, art; the power of performing certain actions, especially as acquired by experience, study or observations.

What does empirical mean; relying on experience or observation alone often without due regard for system and theory. What is science; accumulated and accepted knowledge that has been systematized and formulated with reference to the discovery of general truths of the operation of general laws.

[Slide.]

What is a system: a regularly interacting or interdependent group of items forming a unified whole; an organized set of doctrines, ideas or principles usually intended to explain the arrangements or working of the systematic whole marked by thoroughness and regulatory. What do we mean by risk; risk is the possibility of loss of

injury but also the degree of probability of such loss.

Clearly, I think we have to distinguish between possibility and probability and how do we sort of bring that into focus.

[Slide.]

But, at the heart of the whole debate, I think, what is quality and what is modern quality thinking? Here is some sense of that from eight quality gurus who have tried to define quality.

At the first level, quality is producing products or delivering services whose measurably characteristics satisfy a fixed set of specifications that are usually numerically defined. That is what quality is.

But, at level 2 it is customer satisfaction. In the modern way of thinking in terms of risk, I tend to look at FDA's role in this arena as a surrogate customer for our patients. We are the surrogate customers that have to be--I think satisfying our expectations leads to sort of a risk reduction and so forth. So that would be the sort of debate and discussion that we could have.

[Slide.]

More specific examples of topics that can be brought to this committee include approaches for enhancing the scientific basis of regulatory policies. We can pick topics and have focused discussion and this afternoon, I believe, would be one such example.

Regulatory approaches regarding aseptic manufacturing; I think our goal here is to ensure a sound scientific basis for cGMP inspection practices. The discussion this afternoon will be lead by our GMP colleagues. We haven't seen Joe yet--oh; Joe is here. I was trying to drag on, Joe, to make sure you were here. Joe Famulare will take the lead on the discussion and sort of bring to you their perspective on what are the important aspects here. I am hoping you would give them feedback in terms of how do you focus on science and making sure it is sound scientific basis and not simply going through a process where we have a "check box" exercise.

Science-based risk assessment and management, and so forth. But, also, I think, one opportunity here is to bring controversial topics such as general unresolved scientific technical disputes between industry and FDA. This would be

different from dispute resolution on a company-by-company basis but sort of bring more general issues here.

[Slide.]

What I would like to do; we have invited two guests, Gerry Migliaccio, who will represent PhRMA and Ken Lavin will represent GphA. After you listen to their perspective, if you could give us some input on what our goals and objectives of the subcommittee should be, the process that we have proposed--that is, have a core member group, two members from this advisory committee, maybe eight to ten expert participants representing stakeholders and then use the concept of fact-finding groups or working groups and how would we evaluate the success of this subcommittee.

So I will invite Gerry Migliaccio to sort of share PhRMA's perspective and then the GphA perspective and then your thoughts.

Thanks.

Industry Perspective

PhRMA

MR. MIGLIACCIO: Good morning. Thanks, Ajaz. I would like to thank the committee for inviting me to represent PhRMA to discuss to

proposed Manufacturing Subcommittee. I won't be using slides because they would probably be identical to Ajaz's. We have run into this at many meetings recently.

But PhRMA is extremely optimistic about the FDA's GMP initiative which Ajaz had just outlined. It is a positive step forward in the creation of what we have been advocating which is science-based GMP standards. It allows both FDA and industry to refocus their GMP compliance activities on what is important for fitness for use of the product. So, in other words, it allows us to focus our efforts on the patient.

This committee has been instrumental in promoting process analytical technology. That technology and other innovative technologies that are emerging in the pharmaceutical-manufacturing business have the potential to provide us with significantly more knowledge about the products and processes that we produce and that we use and have the potential to enhance quality assurance.

Now, if you combine those innovative technologies with science-based GMP standards, we truly have revolutionary potential in quality assurance in this industry. But, as in any case

when you have revolutionary potential, it needs to be harnessed, it needs to be guided properly.

I believe that this Manufacturing Subcommittee can play a significant role in guiding efforts around the GMP aspects, particularly the science-based GMP standard aspects of this initiative.

In particular, I believe it will allow both FDA and industry to leverage their resources and to focus them on those things, again, that are critical to the fitness for use of our products.

There are four specific areas where I think the subcommittee can make a significant impact on the GMP initiative. The first area; there will be many opinions about what is most critical in the area of science-based standards. From a PhRMA perspective, we believe that aseptic-manufacturing practices are crying out for science-based guidance.

Other people will have different opinions. This Manufacturing Subcommittee should serve as the steering committee to identify what the most important areas are for science-based standards and to prioritize the work on those. Whether that work is to done at PQRI or elsewhere, someone will need

to prioritize that work and I believe that Manufacturing Subcommittee is the right place for that to be done.

Secondly, as Ajaz talked about risk and risk-based approach, there are going to be many views. There are many views today on what risk-based means, both risk-based GMP compliance and risk-based CMC review. The subcommittee can provide the manufacturing and the quality-assurance perspective on risk-based in the context of those two, the GMP compliance arena and the CMC review.

Again, there will be many other perspectives on that. The common denominator to all those perspectives, again, is fitness for use. But I believe that this subcommittee can perform an important role in bringing together the perspectives of the manufacturing community and the quality community on what mean by risk-based.

The third area, which is--again, Ajaz talked about dispute resolution, what we are mostly calling technical-issues resolution; the subcommittee can play a significant role in the technical-issues resolution process that FDA is currently developing, not as the key player in resolving the issues between a firm and the FDA.

There needs to be an entire process developed for that.

But, just as in pharmaceutical manufacturing, you cannot address a problem or a deviation on its own. Yes; you deal with that deviation but then you have to step back periodically and do a trend analysis where the recurring issues that are cropping up not just in that area but industrywide. So not just with one firm but what is cropping up on an industrywide basis, what are the common issues that we are seeing come into this technical-issues resolution process.

In the early stages of the GMP initiative, the subcommittee evaluating trending what is happening in the technical-issues resolution process is going to identify the need for science-based standards. As we move on and mature in our science-based GMP standards, the trending of what is happening in the technical-issues resolution process will allow the subcommittee to clarify standards, to modify standards as required to meet the needs of what is occurring out there. So I think there is a significant role in that process for the manufacturing subcommittee.

Finally, the subcommittee should continue the work, really the model, that has been set by the Process Analytical Technology Subcommittee. It should serve as the vehicle for the introduction of new technologies in the pharmaceutical manufacturing sector.

There are perceived hurdles. There are perceived regulatory hurdles to introducing new technologies in pharmaceutical manufacturing. Some of those hurdles are valid. Some of them are not. But what there is not today is a forum for addressing new technologies on an industry-wide basis and on an agency-wide basis. The Manufacturing Subcommittee can serve as that forum to evaluate and enable.

The FDA has strongly stated that they do want to enable the introduction of new technologies and this Manufacturing Subcommittee can ensure that they are enabled.

This subcommittee has to have the appropriate expertise to achieve those four roles that I believe it should play. It should have, obviously, the best minds of FDA in this arena but it should also have a broad base of industry representation to ensure that all perspectives are

heard and are provided to the debate.

Representatives from innovator firms in the traditional drug-product sector, the biotechnology sector as well as in the active-pharmaceutical-ingredients sector should participate in this endeavor. PhRMA members stand ready to serve on the committee and we are very supportive of its mission, and we highly endorse the proposal.

Thank you.

DR. LEE: Thank you very much.

Are there any questions? If not, we have Ken Lavin to speak about the GphA Perspective.

Industry Perspective

GphA

MR. LAVIN: Thank you and good morning. On behalf of the GphA, I would like to thank you for allowing me to speak to you regarding this important initiative to enhance the GMP. We believe this program is an important step in clarifying industry's requirements in providing safe, effective as well as affordable pharmaceutical products to the American public.

[Slide.]

We currently believe there exists a wide

array of opinions and actions on the part of the Center and the field on various GMP topics. These opinions and actions also vary from district to district. It is costly for firms to be constantly addressing divergent thinking on these items. One voice and one set of actions by the FDA would further the ability of our companies to address the concerns of the agency.

Inconsistency in inspection and review has let firms to make the most conservative decisions and these may not necessarily be the best decision. This thinking is also limiting to our abilities to add and utilize technologies.

To ensure consistent interpretation and utilization, we believe that the publication of guidance documents will enhance overall compliance and provide clear direction to the industry.

[Slide.]

Some of the areas or topics that we feel should be discussed and the proper guidance provided for are, but not limited to, cleaning validation, process validation, training and vendor qualification.

[Slide.]

Cleaning validation; what is the level of

cleanliness desired? Clarification and true guidance on the use of the matrix approach to cleaning validation is needed. Technologies exist that can monitor and ensure a clean until clean approach. This approach is currently frowned upon. Firms cannot possibly address all the concerns of the Agency without clear guidance on this topic.

In light of the PAT initiative, we urge the FDA to consider this topic in a review of the currently Cleaning Validation Inspection Guidance.

[Slide.]

Process validation; currently firms expend a great deal of time and expense validating their processes. We feel that, while validation is necessary, the information gleaned from these programs could and should be used to lessen the burden on future manufacturing.

This information could lessen our in-process testing regimen. Further, validated process should allow a firm to eliminate unnecessary testing such as blend-uniformity testing.

[Slide.]

Personnel and the training they receive dictate the outcome of many processes. We believe

that the defining document describing the requirements for training and the documentation and tracking of the training all personnel receive is needed. Further clarification on these topics will enhance our abilities to provide the pertinent and up-to-day training our employees require.

Vendor qualification; our vendors of active and inactive ingredients provide us with the materials we need to manufacture quality products. These suppliers are also subject to the same regulatory and inspectional requirements as the finished dosage for manufacturers.

We believe that a guidance document on the qualification of these vendors that allows us to use these supplies and materials with a reduced testing program is warranted. This will allow us to use these materials without adding costs when the majority of the tests needed to release this materials for use have already been performed by qualified manufacturers.

By providing industry with the guidance documents, we believe that the goal of protecting the American public in providing safe, pure and effective products is assured. Industry cooperation and input into these guidance documents

is paramount to the success of this program. Inspection and review based on these documents will provide consistent compliance and provide our industry with the needed information to provide these products.

[Slide.]

The GphA looks forward to continued dialogue on these subjects and supports the endeavor of providing these guidances. We do have members that will sit on any subcommittee as needed.

Thank you.

DR. LEE: Thank you very much. Any immediate questions?

DR. HUSSAIN: I want to introduce Doug Ellsworth who is the District Director from the New Jersey District and Joe Famulare who is the Director of Regional Manufacturing and Product Quality.

DR. MOYE: I believe I understand what vendor qualification is and training. Process validation, I probably need some help on, but I can figure that out. But I don't know at all what cleaning validation is. Can you tell me what that is, please?

MR. LAVIN: Would you like me to answer that?

DR. MOYE: Please.

MR. LAVIN: Cleaning validation is assuring that any material that remains from a previous product and equipment is removed prior to introducing new materials into that equipment. That is done by swabbing or rinsing and then testing the rinse aid or the swabs for the presence of the previous materials.

DR. MOYE: Just to further parade my ignorance, there is no acknowledged industry standard for that; is that right?

LAVIN: No; there is not. There exists a guidance to inspections on cleaning that gives vague references to 10 parts per million or one one-thousandth of a dosage unit, but there are many interpretations by different firms as well as different investigators on what exactly is cleaning.

DR. MOYE: So there is guidance.

LAVIN: Well, there is not really. There are suggestions to guidance. It is not really a guidance document. It is a guide to inspections. It is an FDA internal--

DR. MOYE: I see. So there is not even guidance.

MR. ELLSWORTH: No.

DR. MOYE: When the FDA carries out its inspections, does it find wide variability in cleaning either procedures or cleaning goals? There is no common calibration for cleaning?

MR. FAMULARE: That's correct.

DR. MOYE: Thank you.

MR. FAMULARE: This is an observation that comes up from time to time and there are variations from company to company. I don't have any statistical answer to give you that X number of companies have X number of problems, but it does run the gamut from trying to get down to certain parts per million when going from one process to the other to the extreme where we find API facilities that are manufacturing chemical materials on the same processing equipment as APIs that are intended for human use.

So there is an extreme of findings there.

DR. LEE: Any other questions before we go into the committee discussion?

MR. ELLSWORTH: One comment I would like to make in terms of cleaning-validation guidance.

There are inspection guides, but I think it comes down to the science of how clean is clean. I know there are a number of publications that use different criteria but I think, for investigators in the field, looking at that is whatever scientific justification the term has.

I don't know if FDA has specific, or doesn't have a specific guidance on what should be followed in terms of how clean is clean.

DR. LEE: I think we will come to that later on this morning.

Committee Discussion

DR. LEE: OPS has posed a number of questions for the committee to discuss. I wonder whether we can put this up on the screen again.

[Slide.]

Those are the questions, the goals and objectives, the process and evaluation.

Art, you have been very quiet this morning.

DR. KIBBE: Thank you, Vince. Am I supposed to have an opinion?

DR. LEE: Yes. You always have an opinion.

DR. KIBBE: I had a question for Ajaz. I

was going to catch him afterwards, but, since you put me on the spot. On your third immediate step, it says here, "Having Centers provide a scientific and technology review of all drug cGMP warning letters." What does that really mean?

DR. HUSSAIN: It is a process that we are looking at in terms of issuance of warning letters, having Center input into that more so than we do now.

MR. FAMULARE: I think the real difference in that is, back in 1990, when warning letters began as an entity, they took over from regulatory letters. All regulatory letters were reviewed by a Headquarters unit, whether it be CBER, CDER, CVM. When we want to the warning letter, one of the issues about the issuance of the letters was the efficiency in time and processing them.

We found that it very often took so much time before the letter went through so many levels of review that it wasn't timely. So, direct reference was given to field officers such as Doug Ellsworth's New Jersey District and the nineteen other districts to issue warning letters on GMP deficiencies for dosage-form products.

There are some other examples, but that is

the primary one. What the GMP for the 21st Century is looking at is to--actually, a decision has been made to bring those letters back into Headquarters for technical review, review for consistency. The process is ongoing now to look at doing that and to have the proper resources in place.

DR. KIBBE: When I read it, I was concerned about going back to the situation where it took seven years to get a warning letter out on--I am exaggerating, of course. The understanding I had about warning letters is it was a way of getting the industry to recognize that there was a problem and to get it fixed quickly to minimize the time between an inspector recognizing the possibility of a problem that might impact quality and the industry responding to it so that that window was narrow.

When I read this, I started thinking about that window getting wide again.

MR. FAMULARE: Exactly. We are aware of the balance that we have to strike there to make sure that we get them out quickly. We have to put a system in place that, if we are going to have Headquarters review, we have to do it in a way that they are done quickly or we will not be able to be

effective with them.

But the idea of bringing them into Headquarters review is, again, to promote consistency and technically correct GMP points. That is not to say that all warning letters have those issues, but issues have been brought to light in terms of what one district says versus this other. So we are looking at it from that standpoint.

DR. KIBBE: Just a small aside. I think it is admirable to try to get warning letters as correct as possible before they go out. I would encourage that the Center people spend time educating the inspectors in a way that they share information so that they become comfortable with allowing the inspectors and the field people go to ahead and continue to issue warning letters.

I think we are better served, in a way, to push authority down if we have confidence in the people we are sending out in the field. It kind of sends the message that the Centers aren't confident that the people who are doing the inspections can do a quality inspection and send out a quality letter.

Do you know what I mean?

MR. FAMULARE: I wouldn't take it as a lack of confidence in the field. The important thing is to be able to have proper airing for those difficult or highly technical issues that sometimes need additional input. We want to be able to have the opportunity to provide that.

Doug can address, at the field level, how important it is to get that level of confidence as well with continued hiring and so forth.

ELLSWORTH: I think the issues relating to the warning letter, it is a bigger issue and we are working on improving the communication between technical experts that may be in the Center or elsewhere and the field so that we do have even stronger consistency in our inspectional process even before we get to that warning-letter stage.

DR. LEE: Let me bring the discussion back to the charge to this committee which is to discuss the goals and objectives. I would like to remind the committee that this subcommittee is patterned after the PAT Subcommittee which is now being sunset.

Those of us who were here yesterday and heard the presentation and, at least from our perspectives, the PAT Subcommittee seems to work

quite well. I would like read the slide that Ajaz showed. It is about the science and risk-based approach to product-quality regulation in cooperating an integrated quality-systems approach.

I just want to hear from the committee how you feel about the goals and objectives. Do you have any strong opinions, any advice? Yes, Leon?

MR. SHARGEL: I am in full agreement that the subcommittee is a good idea and science-based guidances and approaches to GMPs is appropriate. I would like the subcommittee to consider something that Mr. Lavin brought up, the level of testing.

In my experience, it is easier to add tests in the field than to take away a test, and to be examining what tests are really necessary. Are we testing too much or are we testing in the right places. As this is evolving, what is the most appropriate way of reaching good-quality products in manufacturing.

DR. LEE: Thank you.

Judy?

DR. BOEHLERT: I would also like to add my support to the concept. I think we heard from DPHA and PhRMA that there is a need for guidance documents. Although they had different areas that

they were focussing on, one on process validation, cleaning validation, the other on PAT and aseptic processing.

Clearly, the need exists. I think the challenge for the committee is going to be to gain consensus on some of those issues because there is a dichotomy between those that want a lot of guidance and those who want to be told what to do but not necessarily how to do it. So that will be a real challenge for the committee.

The other challenge I see is being able to include all the stakeholder groups that you might want. You have generic manufacturers. You have pioneer manufacturers. You have development companies. You have API manufacturers. You have drug-product manufacturers, whether they are conventional or sterile products. You have a lot of different audiences out there.

You have the biotech industry and can you get all the right people together in the same room and yet limit the number of attendees so you don't have a huge committee. So there are going to be some challenges. However, I do support the concept very strongly.

DR. LEE: Efraim?

SHEK: I would like to add a little bit of international flavor to it. In your background, Ajaz, you talk about the international cooperation. We know we have the ICH, of course, going on. But I believe it would be very nice if this subcommittee will have also this aspect. As with their guidance or regulations, science-based are being implemented, that the aspect of international harmonization should be taken into account as many of the companies are becoming global.

The world get smaller. It will be extremely helpful.

DR. LEE: Thank you.

Gloria? Gloria, by the way, is the consumer representative.

DR. ANDERSON: I have been looking through these papers I have here and I can't seem to find the statement of goals and objectives. Can you tell me where that is?

DR. HUSSAIN: The slide No. 4 was essentially the broad goals that sort of we proposed. Our initial thoughts were to use this committee to have input and advice to CDER FDA on science-based CMC and GMP policy development in the manufacturing area. That is the sort core

long-term aspect, but also continue development of the PAT initiative. Then, at least for certain aspects of the cGMP for the 21st Century initiative, itself.

So those are the three broad areas. I didn't call those goals but I think addressing, providing scientific input in those three areas are the goals.

DR. ANDERSON: I would expect the objectives to be a bit more specific. It is difficult for me to comment on them when I don't quite see them. I know what they are for the PAT committee and I think it is commendable that you are going to continue that. But it would be helpful to me if I knew a little bit more about specific detail regarding the objectives.

DR. HUSSAIN: If I may, I did not specifically identify that, but in terms of a bit more specifics, some of the topics for discussion, in my mind, one of the first topics was definitions and sort of common understanding of the terminology, the risk-based approach, what do we mean by risk-based approach in the manufacturing context.

I think we have different perspectives but

don't have a common understanding. So maybe one of the first topics we might pick up is defining these terminologies from different perspectives and sort of moving forward from there. That was sort of one objective, was clarity and definition.

The other objectives that I laid out in my presentation, itself, to start focusing on topics, approaches for enhancing the scientific basis for regulatory policies. An example that this afternoon we will start with that process is the aseptic manufacturing process, itself. So it is sort of staged.

We start out with maybe the fundamental basic definitions and then get into detailed topics for discussion. For those topics, we may need to bring a focused working group because the general, or the core membership of the subcommittee may not be the entire--have the expertise in all given areas.

So that is how we laid that out.

DR. LEE: May I turn the question back to you? What do you think ought to be the objectives?

DR. ANDERSON: I don't think I am in a position to do that. I think somewhere in the document that you have you have defined a problem

and out of that would grow the goals of the committee with some specifics as to how you would achieve those goals.

I usually look at goals and objectives in terms of what I hope to have accomplished at the end of whatever task I am doing. Of course, in my three years on this committee, it seems as if we have never gotten to the end of anything so that may be kind of difficult.

But I don't have any specifics other than those that relate to PAT which I am familiar with. I would be willing to talk with you about them rather than prolong this discussion.

DR. HUSSAIN: Many times, what we do is, for example, we came to fruition yesterday on blend uniformity. Essentially, that topic is completed. We discussed it twice at the advisory committee. The next step is guidance. So most of our end result generally is gathering information and then leading to a guidance document.

So, in the duration of, say, the last three years, if you look at--we finished the guidance on food effects. We finished the guidance on BA/BE. We essentially finished the discussion on blend uniformity. We finished the discussion on

polymorphism. So, in many ways, all these were completed projects.

DR. MEYER: In a sense, Ajaz, I am sure your immediate and intermediate steps are sort of the objectives of the committee.

DR. LEE: Would Gerry and Ken care to comment on the goals and objectives, what you would like to see as the goals and objectives of the committee?

MR. MIGLIACCIO: The four points that I put up are, certainly, from a PhRMA perspective what we would like to see the initial objectives of that committee. Again, to identify and prioritize the areas that require science-based GMP standards, to provide the manufacturing and quality perspectives on risk-based which, as Ajaz has pointed out, is something that needs definition.

Thirdly, to be involved in the technical issues resolution process as in a trend analysis capacity in a clarification of standards. Then, finally, to continue with the PAT model and focus on new technologies. So I think those are four key objectives for the committee.

LAVIN: I think what really should come out is a consensus type of document developed by

FDA and industry on what are the risks, what are the associated risks and what can we do to mitigate those risks. Our businesses are not in business to be noncompliant. That is not what our objectives are.

The FDA does not want that. We don't want that. As an American citizen and a consumer of those products, I don't want that. What we need is a clear set of directives or at least an open dialogue so that we can discuss these things instead of a hit-and-miss approach amongst firms, amongst districts, amongst investigators as well as between the districts and the Centers, themselves.

It is very confusing. Most have a handle on it. Most companies are dealing with that. But, just to be consistent in the approaches and what are the risks and mitigating those risks I think will go a long way to protect the American public.

DR. LEE: Well said. It seems to me the two words that cut across every area is the science and public-health protection. Science, as you know, always moves forward and, therefore, that is the standard is to move in pace with that.

So I think the goals and objectives are things still evolving that we kind of know in our

mind what they could be and I just don't think that we have the time to articulate precisely what those look like. So maybe that would be the first charge to this subcommittee is to clarify the goals and objectives for it. I think that we kind of have sufficient input.

Is there any other discussion?

DR. HUSSAIN: Two points. I think Judy raised a very important issue is the membership and representation. It is a very wide-ranging set of stakeholders and how do we manage that process. Efraim also raised an issue which I think is very important which is international cooperation. My experience with the PAT has been, because of the international membership on that group, in many ways, I think we have achieved harmonization without even talking about the harmonization process.

The reason is I think the science evolved incorporating the perspective from both sides of the Atlantic. So I think that is also a lesson learned and how do we capture that in this if we can.

DR. LEE: Very well. This is a proposal on the screen, two ACPS members. That is it on

this side of the table. And eight to ten expert members representing the stakeholders. Any comments about that?

DR. MEYER: Will FDA be represented, the A stakeholder, or--

DR. HUSSAIN: No; we don't count ourselves as part. We are here to listen and seek advice so we are not in one of those numbers there.

DR. MEYER: Who selects the working groups? These are, I assume, largely in addition to the eight to ten experts?

DR. HUSSAIN: We have some flexibility and we have different processes that we can do this. A subcommittee or a fact-finding group, we can actually appoint and select on our own. We don't have to go through a formal Federal Register process for that.

But, in the PAT subcommittee, what we had done was we had announced in the Federal Register a request for--we defined expertise and we invited people to participate. We had a very large number of applications that came in. So what we did in that case was select a core group and then we invited others who had applied to be a part of the different working groups. That is how we had done

that. But we don't have to have that restrictive process.

Kathy, do you want to say something?

MS. REEDY: The working groups are very flexible. The subcommittees are less so. Two members from the core committee is really the only requirement.

DR. KIBBE: That is a minimum; right?

MS. REEDY: Yes.

DR. LEE: I would like to follow up on what Marv said, whether or not there ought to be representation from the agency as some kind of a staff liaison.

DR. HUSSAIN: Could you repeat that?

DR. LEE: I think, in some organizations, you always have, let's say--let me point out the organization I know a little bit about is AAPS. There are a number of committees and each committee is supported by a staff member who is a resource. So that person is going to go get the information, get things done, that sort of thing.

DR. HUSSAIN: What we plan to do is we don't want to burden our Advisors and Consultants staff to that degree. So, what we have tried to do is try to help them--actually, with the PAT groups

and so forth, OPS has been providing some logistic support also so we will try to do the same thing. I think the Advisors and Consultants staffs are doing such a good job already, but their resources are limited. So we will have some other liaisons identified.

Marilyn is a liaison from OPS for this committee. We will create someone like that for the working groups and so forth, also.

DR. LEE: She is a superwoman.

Any other comments about this makeup, the two ACPS members?

DR. SHEK: If I may. One aspect, when you are going to make the decision look at the expert. I am looking at the title of the committee, Manufacturing. If you look at the goals, I think it is more CMC-type of a subcommittee. It is so purely, I believe, manufacturing.

As we looked, I think, at the experts, we should make sure that part of the stakeholders are coming from the R&D environment. Since they are basically GMP regulations from Phase I clinical studies, people are involved purely with the regulations. But there is also the aspect of the future and new technology coming in.

I think PAT is a good example where the push didn't come really from even R&D. It came from manufacturing, or not from the industry. In the future, it would be nice if we can turn it around. So, at least some of those eight to ten should come from an R&D environment.

DR. HUSSAIN: After I put the slide, it occurred to me I missed the R&D group. I just had manufacturing and quality assurance, but I think, unless you have the R&D part of that--I think it is important. Thanks.

DR. KIBBE: Just a couple of things. I think that this subcommittee has an opportunity in front of it to basically change the way both the Agency and the industry work in a lot of ways and have a long-term impact.

Changes could be advantageous for the industry in terms of efficiency, advantageous to the public in terms of better assurance. I am still struggling about making sure we have all the stakeholders and all the people involved and, at the same time, having all the expertise. It is clear that we need to have, at each one of our meetings, someone from the Agency that represents the field as well as someone from the Centers

because the field is going to have to activate what is going on at the same time.

It is clear that there are different concerns from different aspect of the industry but, at the same time, there are concerns from the people who are manufacturing testing equipment. We get a lot of good input in terms of PAT from them. And the international community that might be ahead of the curve on some things, behind the curve on others. I do respond quite positively to the comments that, while we were developing that, because we had an international flavor to it, harmonization came along as a consequence of fallout.

So I don't know how you are going to be able to pack all of that into eight people. I am worrying about making sure that we get the right mix and we have the right group, and then your time lines to get some of things done. We also need to get a real vision for the committee because of its potential large impact and goals and objectives.

It is going to be a daunting process the next couple of years.

DR. LEE: You might be the one we would ask to chair it, Art.

DR. KIBBE: I love daunting projects.

DR. LEE: As we discussed, the committee is extremely important and I think that we need to give it some careful thought about how to constitute it, to make sure it is a progressive committee. I think something I liked hearing this morning is that someone should be looking out to the future. Is that the charge within this committee? I think so. I think this should be looked at in order to mix housekeeping and forward-looking activities in the same committee is something that you might want to consider.

I am getting off the committee so I just would make a laundry list for my successors.

Any other suggestions? What does OPS expect from this committee?

DR. HUSSAIN: What we will plan to do is, in a sense, take the input and start working towards forming this committee and then go through the process that is needed to do that. Again, I think going through the PAT subcommittee helped because if you look, on my right, you have Doug and Joe always with us on the PAT so the process worked very well. I think we want to sort of repeat that success again.

Clearly, I think that this is not just CDER now. CVM, CBER and everybody--everybody has to be together on this. So it is a bigger challenge definitely than PAT, but I think going through that PAT process helped us at least create the part that will lead us to helping manage this more complex one.

DR. LEE: Just for clarification, Ajaz, the ACPS members are by statute?

MS. REEDY: Yes; at least two members.

DR. LEE: At least two; okay.

DR. MEYER: For the experts, do you have the eight to ten--do you have to have geographic distribution and ethnic distribution and gender distribution or can you pick eight females that are experts from Merck?

DR. LEE: What's wrong with that?

DR. HUSSAIN: We always try to go for diversity. That is always our goal. Definitely, I think that is mandated for the advisory committee, but I think it is a bit more flexible on that. But that is always our goal, to go for diversity as much as possible.

DR. LEE: Working groups.

DR. HUSSAIN: In terms of working groups,

I think what our thoughts were--for example, if I take the example of cleaning validation, it is a very focused topic. I think there is a need for guidance there. If I use that as an example, then the working group on cleaning validation would be sort of a fact-finding and making certain recommendations to the committee could be formulated and asked to do something rather quickly and come up with something, and so forth. So that would be an example.

But I think the numbers and the topics, I think I like what Gerry mentioned as part of the goal of the subcommittee is to identify these topics and prioritize them because there are many topics to be addressed. I don't think FDA has all the resources to start everything at the same time, so we have to manage that process well.

So one of the charges of the first meeting of this subcommittee would be to simply identify those topics, prioritize and then, as part of the goals and objectives setting itself. So that is how we intend to proceed.

DR. LEE: Gerry, did you want to make comments?

MR. MIGLIACCIO: I would be happy to

provide PhRMA's list of priorities to Ajaz to focus on. We have gone through that prioritization exercise. We have polled the entire PhRMA membership and I think there will be a lot of commonality from what you are thinking and what we are thinking.

DR. LEE: Anything else about the process?

DR. HUSSAIN: This is with the endorsement of that, and I think we can start taking input we have received and move forward.

DR. LEE: It is still not clear to me who is appointing the members. The OPS?

DR. HUSSAIN: We will work within FDA to bring that together. It will not just be OPS. It is the Office of Compliance and will involve other segments like Doug and other districts. So it is sort of a team process.

DR. LEE: Thank you.

Gloria?

DR. ANDERSON: I would just like to suggest that, prior to asking the committee, after you have formed it, to formulate the goals and objectives. It seems to me like someone would need to take a cut a doing a first draft because it is not clear to me how you will know what your

membership would look like if you haven't formulated clearly in your mind what the task is that the committee will do.

DR. HUSSAIN: In many ways, I think the manufacturing--the scope of the problem ranges from R&D to manufacturing to QA functions. So, in that sense, we think we have clearly identified what type of expertise and experience is needed.

I think the challenge would be the stakeholders because the number of stakeholders are many in the sense--I mean, we have two stakeholders represented here from the PhRMA and GphA but that is that is not a complete list of stakeholders. That will be a challenge, I think. That will be sort of an internal discussion and decision then.

DR. LEE: Evaluation.

DR. HUSSAIN: The evaluation, more I meant it--it is sort of reporting back to this advisory committee, itself. PAT kept receiving good timely feedback in terms of that. So it is continuing that process. If you have any thoughts on how we could have improved the PAT process, itself, that would be a sort of a question on evaluation on the PAT subcommittee, itself, from your perspective what we could have done better that will help us.

DR. LEE: Gloria?

DR. ANDERSON: I would like to suggest on the PAT, and this has always concerned me, is that I don't think we went back to the original goals and objectives enough to see where we were. At the last committee meeting, I suggested that now that we are as far along as we are with the task that was set out at the beginning, that it might be a good time to go back and see where we are and make some determination about how to proceed in the future.

I think that would be a good thing to do with this, particularly in terms of evaluation because I always look at evaluations as a means of determining the extent to which the goals and objectives have been or are being achieved.

DR. KIBBE: I think this particular committee is such a broad-impact full committee that we probably, after we get some general guidance from the agency on the overall mission or vision and begin to set goals and objectives, we are going to have to set milestones timely as we look at each aspect that we are trying to look at, if we are going to work in one particular area to start with and move through it.

I think Gloria is right. Closing the loop with advisory committees sometimes, as you said, "Well, we took all that information and guidances are coming." I think the committee would like to see the guidance when it actually happened so that we knew that what we did had an outcome that was tangible and useful.

Quite honestly, one of the things that I would like to see us do is survey our stakeholders independent of the committee for the impact of what is going on, maybe pre or post kinds of things, where we get a sense of what the industry thinks is happening today and then, two years from now what the industry thinks has changed and what has happened. That might be helpful, too.

DR. MEYER: A follow up on Art's comment. If I have a student prepare an exam for me and I grade that exam, I have evaluated them. But, if I don't show them what grade they have, they don't know how they did. I think that is missing to some extent in the activities of this committee. So if the subcommittees prepare something for this committee, this committee then talks about it for two days and Ajaz takes it and throws it in the basket, we would never really know that. It just

kind of disappears into the future.

It might be useful for the beginning of each session of one of these committees, or this committee, to have kind of a review; this said to this and this said to us and we thought it was a crock, or we have put forth a guidance.

DR. HUSSAIN: I think it is a very good point. In fact, it was raised yesterday. Dr. Lee is--sort of this is his last meeting and he has been the chair for a relatively short time. Some of the things we have started, he will not know what happened with them unless he comes back to FDA to find out.

DR. LEE: I don't want to know.

DR. ANDERSON: Also, I think as new members come in, I sort of look back at the memo I sent to you. I have the transcripts listed, the web addresses. But the transcripts may not always provide the summary that is need to keep the continuity. I think we will try to find some means of doing that.

DR. LEE: Very well. I think we have had some good discussion. I think the folks around the table probably will know exactly what to do. I think this is a very important subcommittee, an

experiment in extension. I emphasize that the basis is science, risk-based, quality and also I will add some common sense.

With that in mind, are there any questions before we take a recess? If not, let's continue at 10 o'clock. Thank you.

[Break.]

Manufacturing Issues

Sterile Drug Products Produced by Aseptic Processing

DR. LEE: We have some presentations on manufacturing issues, sterile drug products produced by aseptic processing. Ajaz, are you going to give the introduction?

Introduction

DR. HUSSAIN: My introduction is a brief introduction. Actually, I just wanted to introduce Joe Famulare. He is going to take the lead to introduce the topic. Just two perspectives I want to share with you. This is probably the first manufacturing topic in this format that we have brought to this committee so it is sort of a new format. Also, what we are trying to do here is to bring all segments of the FDA which impact on this topic.

So you are looking at Jay from CBER, Joe from CDER and Doug Ellsworth from the District representing those segments. The Office of Pharmaceutical Science, the Microbiology staff will make a presentation, a brief presentation, on how we are planning to support this initiative. So I think our goal here is to sort of listen to the Advisory Committee after they have a chance to listen to the issues being presented here.

So, with that, I will introduce Joe Famulare.

DR. LEE: Thank you.

MR. FAMULARE: Thank you and good morning.

[Slide.]

I just wanted to address this Advisory Committee to address the topic of aseptic processing standards today for a number of reasons. The most prominent of these is the urgent need to publish guidance that could promote better understanding of some basic cGMP issues relating to aseptic processes.

As we reviewed our program for the inspection of drug manufacturers from a risk-based perspective, we have agreed that sterile drugs are, in many respects, the highest risk category due to

the route of administration and the potential for hazard to the patient. Our 1987 guidance entitled, Sterile Drug Products Produced by Aseptic Processing, noticed that the Agency would issue revisions in the document from time to time when it recognized the need.

Through the regulatory efforts and comments submitted by interested persons, with this knowledge, the following evolution and technology stand as an understanding of aseptic processes, we embarked on the task of updating this 1987 guidance in 1997. The intention of the revision was to improve clarity and explanation of cGMP issues to better facilitate industry compliance.

[Slide.]

This effort, as Ajaz mentioned, is a joint CDER, CBER and ORA work product. We have here, of course, Doug Ellsworth representing the Field Drug Committee in ORA, the field, and Jay Elterman from CBER, the Director of the Division of Manufacturing of Product Quality in that unit.

The overarching goal of FDA in issuing revised guidance is to provide a document that will facilitate improved industry compliance. We receive questions on practical and technical issues

that have formed a clear pattern and plan to overlap very much with issues that are very often cited in regulatory citations, whether they be 483s or warning letters.

We want to bring clarity to these quality issues that are sometimes murky by providing sound understandable principles and without being overly prescriptive. We are providing this unprecedented opportunity for a preview of our current thinking because we believe it is urgent for guidance on aseptic processing to issue.

Thus, we have this concept paper here today to solicit feedback and we are trying to take in all the comments from this advisory committee in order to publish the draft guidance as the next step.

[Slide.]

Just to cover the concept paper, one of the basic things that we did was to improve the format over the 1987 Guidance. Hopefully, it is more user-friendly with a table of contents and headings and easy to read and follow. We have added definitions of air-lock components, colony-forming units, dynamic conditions, endotoxin, gowning qualifications, barrier and

isolator technologies, et cetera, so that we wanted to bring things in line with today's current technologies.

We have also updated old sections. One of the areas, of course, would be the evolution of the sterility testing in the USP. And we have added some new sections, again based on advances of technology and dealing with issues that we see as needing the most guidance such as personnel, the use of isolators and early processing steps are particularly a concern to the biologic industry.

[Slide.]

This guidance has been requested by the industry. Again, we hope to promote better understanding of GMPs. Industry organizations such as PhRMA and PDA have requested updating guidance on an expedited basis to address areas where there is confusion on what the minimal GMP standards are. FDA, of course, agrees that we wanted to provide this guidance.

By having proactive communication of our expectations, we hope for firms that are building or modifying facilities to do that in an efficient, money-saving way, and to, again, clarify issues where questions persist.

[Slide.]

In answering the question why to improve the guidance, it is important to reflect the evolution of knowledge, remove that information that is obsolete from our 1987 Guide that is out there, and fill major voids that have been illuminated over time. We want to reflect current standards and, importantly, we want to incorporate the latest scientific principles.

[Slide.]

We want to reflect uniformity between the Discussions and Biologics Center and, of course, have the field represented well in terms of the implementation by field investigators in looking at aseptic process manufacturing. We want to move forward on those issues that have been debated year after year in working together on new matters of importance so that the most important issues are covered during our inspections and are given emphasis by companies.

[Slide.]

Going back in a little bit of history, the original 1987 Guidance was written in lieu of regulations and the process began, really, around 1980. In the Preamble of the GMP regulations of

1978, it said that, while the GMP regulations address finished dosage-form drugs, that many unique and critical variables attendant to sterile drug manufacturing would be best addressed thought the publication of additional regulations on both SVPs and LVP; that is small-volume parenterals and large-volume parenterals.

Most of you know that FDA ultimately wrote regulations for LVPs but they were never finalized. In lieu of the regulations, of course we provided the Aseptic Processing Guidance of 1987. The choice of the guidance route, we hope provided industry with a better understanding of FDA's interpretations of the regulations while still leaving significant flexibility for manufacturers by virtue of not establishing mandatory standards.

That 1987 guidance, we believe, proved effective in answering some recurrent questions at the time but, over the last several years, we have recognized the gap of updated cGMP guidance in high-risk areas of sterile drugs. Industry representatives have repeatedly asked for the issuance of this document since our inception of announcing that we were working on this.

[Slide.]

It is important to address the quality of sterile drugs as a priority for the Agency. One of the reasons that, of course, this ends up as being one of the first things that we look at, as we look at the formulation of this new manufacturing subcommittee. We see that there are persistent problems that need to be resolved and averted in the first place.

It is very important to maintain a steady supply of many of these drugs to the American public. We see that they represent very important therapies. Very often parenteral manufactured products end up being areas where we have shortages and there has certainly been publicity in the recent year or so, whether it be certain biologic products such as flu vaccine and other types of vaccine products that not only are important therapies but are also national security concerns.

So it is important to have this area covered in a way to avert these problems in the first place. Of course, handling these in the regulatory mode is a time-consuming problem for both FDA and the industry.

So we are hoping to have better adherence to cGMPs for sterile products through improved

guidance, improved inspectional focus and better understanding of the scientific principles.

[Slide.]

We could see, in looking at the recalls from Fiscal Years '99 through 2002, that certainly lack of sterility assurance has represented a large number of recalls that have occurred over these last couple of fiscal years so, again, reinforcing the need to avert these problems and to find out what the problems are in advance and to work through this guidance in identifying those areas where we could give the best guidance to avert these types of problems.

Many of these result as an outcome of cGMP inspections. You can see, just looking at Fiscal Year 2002, we ended with some 52 recalls in this particular area.

DR. MOYE: Could I ask just a clarification while that slide is up? What do the colors mean?

MR. FAMULARE: They just distinguish the different years.

DR. MOYE: They were all blue except for the last two.

MR. FAMULARE: There is no other meaning

other than to distinguish the two years. I apologize for not having a consistent pattern of thought for the colors.

DR. MOYE: That's all right. I just didn't want to miss anything.

DR. KIBBE: Is there an explanation for the dramatic change between '98 and '99?

MR. FAMULARE: Many of these result as a result of cGMP inspections that have occurred. In one particular instance, and this is top of my head, I think one company that was under a regulatory concept decree actually cleaned up the marketplace of their products rather than to try and evaluate all the different sterility problems that may have occurred from products that they were, overall, eliminating from the marketplace.

So, as a matter of expediting removal of suspect products, the company removed them all and each product represents a separate recall incident. So it is not companies, per se, but individual products.

Any other questions on this slide?

[Slide.]

Important to consider for aseptic processing is that there are many variables that

occur in aseptic processing. So, in preparing this guidance, we had in mind that aseptic processing requires daily vigilance and attention to many details which is certainly a true test of cGMP conformance.

Adherence to procedures and details is important and fundamental to sterility assurance. Process consistency in aseptic processing is of utmost importance. An overriding objective, of course, is that each unit produced in a batch be free of microorganisms.

In looking at sterile drugs, in terms of our risk-based approach, as Ajaz mentioned in looking at the goals of the cGMPs for the 21st Century, as a product class, of course, sterile drugs can represent hazards to a patient and an unacceptable risk to patients that may be posed by contaminated drugs.

[Slide.]

Failure to adhere to cGMPs in the instance of aseptic processing can have an impact on product safety and efficacy and, therefore, this whole category of drugs is a top priority for inspectional coverage is a risk-based inspection approach.

[Slide.]

In looking at the risk-based approach, we need to analyze what are the causes of contamination and where are the potential roots of contaminations in a firm's process. We need to focus in our guidance on the issues of most concern, those critical control points. So these are the areas that we will be looking for comment as individuals have looked at the concept paper that we have put out there to see that we have put proper emphasis on these issues of most concern.

[Slide.]

Good science, of course, again, a recurring theme of today in focussing on these issues. We want to have a scientific-based approach to cGMP emphasized in the concept paper. In putting together this paper, there were certain key sources that were looked at; scientific journals, technical documents, various textbooks, vector illuminated by facility-contamination findings when we actually had the opportunity, as FDA investigators or even as people in the Office of Compliance that review the results of these investigation reports, have actually had hands-on experience in seeing what the results of those

investigations are and what the findings of contamination have been.

Very importantly, we hope to have captured within this document the results of our cGMP case reviews and the many cases that we have looked at, both particularly CDER and CBER, at our level, to see what the commonalities were, to see what those areas of emphasis need to be which led to our regulatory entanglement so that we could take that experience and bring it forth into this concept paper and eventually into guidance to address those issues.

[Slide.]

I will just briefly--Ajaz went over this in great detail this morning--the cGMP for the 21st Century to make sure that, as we look at this concept paper that will eventually be our guidance, that we outline the risk-based approaches that will better focus FDA's and industry's resources, we make, as is noted in this concept paper, a good system better, focus on critical process parameters, critical control points and yet be flexible enough to encourage innovation in the industry.

So, while these are the major goals of the

cGMP for the 21st Century Program that was announced this past August by the agency, we want folks to keep this in mind in looking at the concept paper, that we keep sight of theses goals as we put forward our ideas in this concept paper.

[Slide.]

We have to recognize the diverse nature of the industry and that new guidance will address this essential practicality while also providing meaningful insight into what FDA's expectations are. We need to encourage innovation by acknowledging new technologies and by liberalizing some old standards where it is appropriate.

For example, in one of the examples that I could think of in the concept paper where we had a specific number for the rate of air flow, now this could very often be demonstrated by smoke studies. It is important to remember, again, and I know we say this every time FDA issues a guidance but I will emphasize it again, that this will be a guidance and not a regulation so there is latitude for flexibility.

[Slide.]

So, to focus on today's broad question in looking at this concept paper. What additional

considerations are needed to ensure that the proposed guidance contributes to the improvement of the aseptic manufacturing process across the industry, improves consistency in the FDA inspection process, and, at the same time, can encourage innovation in the aseptic-process manufacturing arena.

[Slide.]

Continuing our broad questions, is FDA's current thinking on these topics as outlined in the concept paper well grounded in science and sufficiently detailed to provide industry with clarity on FDA's expectations with respect to assuring appropriate quality of sterile drugs by aseptic processing?

[Slide.]

We see, again, a compelling need for this revision to the 1987 guidance. The concept paper represents our current thinking to date and we really value your feedback, particularly on the level of specificity. There is always debate as to whether we have targeted what we are looking for too specifically and, at the same time, allowed latitude for individual innovation or individual firms' needs.

We will listen carefully and do a comprehensive review of all the advisory comments and, of course, then we will take this advice and be able to put this best effort as the results of the comments we get from the advisory-committee setting here today into publishing a draft for public comment.

I just want to end by thanking all the internal constituents within FDA that have worked very diligently. As you see, the project started in 1997 in order to gain a consensus within FDA to put out this concept paper. Those are the various groups with CDER, OPS and OC, ORA and CBER.

Thank you.

DR. LEE: Thank, you, Joe.

Any immediate questions?

DR. HUSSAIN: Joe, if you want, or I think we need to introduce the invited guests to this section.

MR. FAMULARE: Okay. We will have, as speakers, and I don't have the names in front of me except right over here, various representatives of the FDA to introduce various topics or subjects throughout the day. But we also have some invited guests such as from the PDA, Russ Madsen who will

be talking this morning, giving the PDA perspective.

We have Berit Reinmuller who will be giving a technology presentation on air flow and air velocity. And then we will have various FDA individuals really serve to structure the topics of the day. Actually, the next presenter will be Rick Friedman who will set the stage for the various issues, the five main issues, that will be covered out of the guidance.

Not to steal his thunder, I will let him introduce those topics, but he will be the first speaker broadly introducing those topics. He will be back again this afternoon to introduce one of the five topics along with Kris Evans from ORA, Bob Sausville from CBER and Brenda Uratani from CDER Compliance. Again, representing the collaboration on this document, we will have from OPS, from the review side, also giving a brief presentation on the interrelationship of the review and the GMP side, David Hussong.

Did I forget any names, Ajaz?

DR. HUSSAIN: Also, I think if you could just go around the table and introduce the new invited guests, also.

MR. FAMULARE: Okay.

DR. LEE: Or we could have them identify themselves.

MR. FAMULARE: Oh; the other guests? I don't have the list in front of me. Those guests. That would be easier just because I don't have the names in front of me. I'm sorry.

MR. MUNSON: Terry Munson. I am a consultant from KMI/Parexel. Was ex-FDA, worked in the Office of Compliance at CDER.

MS. LOWERY: Sandi Lowery, a consultant from Quality Systems Consulting.

DR. BURSTYN: I am Don Burstyn from Alkermes Pharmaceutical Developer and Manufacturer.

MS. DIXON: I am Ann Marie Dixon from Clean Room Management Associates. I am a consultant.

DR. KORCZYNSKI: Michael Korczynski, Principal, Mikkor Enterprises.

DR. LEE: And Professor Reinmuller from Stockholm?

DR. REINMULLER: Berit Reinmuller from the Royal Institute of Technology in Stockholm, Sweden.

MR. MADSEN: Russ Madsen from PDA.

DR. LJUNGQVIST: Bengt Ljungqvist, from

the same university as Berit Reinmuller.

DR. LEE: I think that covers just about everybody before lunch. Thank you.

MR. FAMULARE: Rick Friedman will be the next presenter. One of the other guests is Jeanne Moldenhauer.

DR. LEE: It is hard for me to keep track of all these names.

Rick, you have twenty-five minutes.

Contamination

MR. FRIEDMAN: Thank you and good morning. My name is Rick Friedman. I work for the Center for Drugs, Office of Compliance.

[Slide.]

Aseptic processing is an intricate and complex method of producing sterile medicines. Since the publication of the 1987 Guidance Document, there has been an evolution in the knowledge and understanding of aseptic processing. Data-analysis experiences shared through pharmaceutical-industry publications and conferences have contributed significantly to this enhanced understanding.

CDER, CBER and ORA have issued a joint concept paper for your consideration that

comprehensively outlines the cGMP areas that we believe are in most need of guidance. The cGMP specifically addressed the need to monitor and control sources of variability in the manufacturing process. GMP representatives throughout FDA regularly speak of identifying the critical control points for a given process and the need to support the process with well-conceived design control and maintenance procedures.

Using this mind-set of sources of variability and critical control points, our concept paper stresses major indicators of quality for an aseptically processed parenteral drug.

These key determinants of sterile drug quality also make up the main theme of this presentation which will provide a bit of the theory and practice that have formed the foundation of our current thinking.

After discussing some of the science base, I will address the practice through sharing a few case studies that illustrate where one or more critical control points failed with the consequence of nonsterility.

[Slide.]

It is very difficult to quantify risk but

there are a number of useful tools in the literature describing metrics often used by the pharmaceutical industry. One method is discussed by Paul Noble in the July or August 2001 PDA Journal. He uses the popular failure mode and effects analysis, FMEA, method to indicate which parts of a firm's operations present most GMP and public-health risk and, therefore, deserve the greatest attention.

In discussing the three aspects of this method, he starts with the first component, reducing the severity of risk by process changes or product redesign. He states an example of reducing risk severity would be exploring development of a terminal sterilization process for a product that is aseptically produced.

The second component of this method is reducing the probability of occurrence of risk. Noble states that these improvements can have "long-lasting benefits" including efficiency gains and avoiding future problems. He names the following systemic improvements; "process automation, tighter controls upstream in the process and implementing new technologies such as isolators to reduce the chance of microbiological

contamination."

He then discusses the third category, the detection of failures. He characterizes validation tests as "intensified monitoring"--that is a great definition of validation--"which should detect flaws or weaknesses which may not be normally observable. A media fill is a good example of a validation test."

He notes that, "Conducting a medial fill will not, by itself, reduce the chance of contamination. Only a proper corrective action response to the detected flaw or weakness will do so." We found it notable that these examples named by the author as beneficial in preventing the costs associated with product-quality problems also happen to mirror the many principles included in our concept paper and these issues will be among our major topics of discussion today.

[Slide.]

Our revision of the aseptic-processing document began by asking this basic cGMP risk question; what are the potential sources of contamination in an aseptic process? In an effort to answer this question, the concept paper focuses on selected aspects of the aseptic process and

facility that, if not maintained in a good state of control, can lead to the contamination of finished units of a parenteral drug.

We also asked the question, what measurements are most valuable in indicating sterility assurance. While cognizant that some factors of the manufacture of a drug are more influential than others, they get different weights, we acknowledge what so many before us have also acknowledged, that, if an aseptic-process operation does remain in control throughout processing, contamination may occur that is unlikely to be detected in the end-product sterility test of a very small number of units.

Instead, there are number of personnel, environmental and mechanical variables that must be considered to make a reliable assessment of whether the aseptic operation is under control.

We also concluded that such metrics should be founded in scientifically sound in sufficiently representative sampling plans so that meaningful data can be used to evaluate whether a batch was produced under adequate conditions. We felt that we should focus on those metrics that can provide a signal of an emerging or existing route of

contamination.

In short, our compound addresses areas of GMP that, if not controlled, can impact on drug safety and efficacy and we will not need to go into explanation for the group assembled today regarding the fact that parenterals contaminated due to poor manufacturing conditions have, in fact, led to infections.

[Slide.]

This slide is an attempt to visually illustrate the complexities of aseptic processing. One might call it a macro-model of daily "sterility assurance," and sterility assurance is in quotes because we know the difference, obviously, between SAL, sterility assurance level, which is predictable in internal sterilization and the vagaries of aseptic processing.

This macro-model of daily "sterility assurance" includes the big-ticket facility and process-control factors that form the basis of overall process control. The first influential cGMP element is personnel--I will go around clockwise and maybe give an example or two quickly--but, personnel, facility and room. The D and M mean design and maintenance. The kind of

question we would ask from a GMP perspective is is the facility constructed to accommodate the constant dynamic interaction between rooms and does the design create contamination routes. Is an adequate maintenance program in place to address the gradual breakdowns in facility infrastructure.

Aseptic processing line design and maintenance process--this refers to both the filling process and the unit-sterilization operations that support it, autoclaving, et cetera, dry-heat depyrogenation. Does personnel and material flow through the facility increase the chance for tracking contaminants into the aseptic-processing room? Do the ergonomics of process flow or equipment configuration create difficult aseptic manipulations, unnecessary activities too close to the aseptic zone or other issues which undermine confidence in the sterility of each unit?

HVAC and utilities; response to deviations and environmental control trends; disinfection regimen and actual practices, media fills; and, of course, the essential role played by the quality assurance and quality-control units.

[Slide.]

So there are a number of potential sources of contamination that must be addressed in accord of cGMP. The existence of these many interdependent sources of variability are succinctly summed up in this excerpt from ISPE's Sterile Facility Guide which emphasizes that the aseptic-processing room does not exist in a vacuum. The room is part of a dynamic integrated system that is affected by the activities that take place both within it and around it. As such, they write that a firm must employ, "a strict design regime not only in the process area but the interactions with surrounding areas and movement of people, materials and equipment so as not to compromise aseptic conditions."

In other words, the microcontamination can eventually migrate to the critical zone and cause product nonsterility if attention is not paid to the holistic design, control and maintenance of the facility.

[Slide.]

There will be a lot of discussion today about environmental-control design and, of course, personnel. So let's look closer at some quotes from journals and textbooks of the topics of

personnel design and environmental control. Even with a good facility and processing line design, poor personnel practices can upset the delicate balance of the aseptic operation. With regard to aseptic interventions, our '87 Aseptic Guidance points out that any manipulation of the sterile dosage-form containers and closures involves the risk of contamination and, thus, must be carefully controlled.

The late Professor Kenneth Avis of the University of Tennessee spoke about the need for "continued vigilance throughout the entire manufacturing process" back in 1971 in the PDA Journal. The researchers Ljungqvist and Reinmuller state, in their textbook, Minimizing Contamination Through Proper Design, that, "Unstable situations are, in most cases, caused by the influence of arms and hands."

We are pleased that Ljungqvist and Reinmuller, whose research has been widely cited by industry and regulatory authorities alike could travel here from Sweden to discuss their research today. They have made a significant contribution to parenteral science in their studies of the influence of design, personnel practices and

environmental control on product contamination.

[Slide.]

Here are a couple of references on environmental control. Let's look at the second one. Sinclair and Tallantire performed studies to determine if a correlation between Class 100 control and contamination prevention exists. Using a blow-field-seal line, BFS line, and a known microbiological challenge level, this research team established that there was a "definable direct relationship between the fraction of product contaminated in the lot and the level of microorganisms in the air surrounding the machine."

This type of basic research study is useful in that it showed a correlation between an increasing number of microcontaminated units and the degree of contamination in the immediately adjacent machine containment room.

[Slide.]

Among the recommendations was that local protection of the operation could be improved to make contamination risk to the filling step more independent from the adjacent operation, the adjacent environment. Sinclair and Tallantire also found that product protection at lower velocities

was inadequate to prevent contamination. As velocity increased in this system, the number of nonsterile units decreased.

They conclude, for the systems studied, "a reduction in contamination of blow-field-seal product is achieved by a 'high-quality and high-volume air shower to protect the filling zone.'"

I have just reviewed just some of the numerous useful references that are relevant to our discussion today. Based on these and many other references, there is concrete foundation in the Year 2002 for the statement that, "Design, environmental control and personnel practices are each crucial to an aseptic processing operation."

You might ask, at this point, how does this statement of theory correspond to our actual experiences with industrial-contamination problems? The answer to this question is that we see a cross-section of sterility failures each year that illuminate commonalities in the source of contamination. Lack of adherence to cGMP in one or a combination of these three areas has been central to the vast number of these.

This brings us to some case studies that

illustrate the origins of some of these contamination problems. Some have asked the question, what makes three validation batches so special. Why not one, or five or ten? A three-lot study may, indeed, not be perfect but it does generally provide a reasonable degree of reproducibility given practical and business limitations.

A commercial process is tested with three different lots, each with their own unique variables presented by a given day in it is somewhat unpredictable events and, if done well, at the conclusion of the three-batch study, a more enlightened understanding of the state of commercial process control will be gained.

[Slide.]

This case study is a good illustration of the value of showing reproducibility. In this case, a firm had a pristine clean facility for two or three years, no media-fill failures. It is a large manufacturer. And then, one day, it had a media-fill failure where approximately 60 percent of the vials were contaminated.

The failure was considered to be a spurious event. Nonetheless, there were some

corrections that were made to the firm's satisfaction to improve different areas which were thought to, in fact, correct the issue.

The firm looked at the FDA guideline and PDA's Technical Report No. 22--both note that three lots are needed if a line falls out of qualification--for revalidation. So they ran the first media-fill batch and found no contamination.

They ran a second media-fill batch and this one was over 95 percent contaminated over 5,000 vials. The third media-fill batch was run. No contamination. So, one can see, if one batch was run, a firm would return to production and release of commercial lots without knowledge that a nonsterility problem still existed.

The root cause in this case had to do with personnel. Isolates in both failures, both of the media-fill failures, were common skin-borne microbes. They found that the gowning level was inadequate. Part of gown was nonsterile and the sleeves were sterile and maybe other parts of the gown were also sterile. But part of the gown was nonsterile and they felt that the aseptic technique was questionable and there was also some skin exposed.

Now, work was being done under a hood so presumably, by doing the work under the hood with sterile sleeves and sterile gloves, there wouldn't be contamination. But, obviously, this underscores the importance of full gowning and the fact that touch contamination and cross contamination from nonsterile and sterile parts of the gown is a practical reality.

The corrections to resolve these issues in this case were enhanced personnel and environmental monitoring performed in the near term. But the firm did, and one of the things that we are stressing in this guidance, increase in automation, removing personnel as much as possible from the aseptic processing by later modifying the line to allow for sterilization in place. They no longer have an aseptic connection. So they have taken that risk out of the process.

[Slide.]

This recent case study occurred at a major manufacturer, also. During the inspection of this facility, the inspection team actually entered the clean room on a nonproduction day and found mold in the aseptic-processing room. Mold had built up in between two walls in which the return vent was

located.

The investigators observed a significant area covered with greenish hard, dry mold drippings that extended out of the vents. It was evident to them that this visible mold buildup in the air returns should have been readily noticed and it appeared that it had been there for quite a while.

The firm had validated a number of sterility failures without an adequate basis, a laboratory causality. In addition to the highly unusual event of our investigators seeing the mold in the room during the inspection, the firm had detected a clear adverse trend showing persistent mold contamination in the area during environmental monitoring. The firm had a trend of several sterility failures and the inspection team found that the same molds found in the environment were also named as isolates in the sterility test positives.

[Slide.]

Here is an abbreviated summary of some more cases where adequate procedures were not followed to prevent microcontamination. The origins of contamination listed on the next two slides are those named in the firm's actual written

or media-fill and sterility-failure investigations.

Just to go through these quickly. Aseptic practices is named very frequently in media fill and sterility failures. Personnel returned after a long winter shutdown. We have seen this scenario repeated a few times over the years. There might not be the currency of knowledge coming right back from a one or two-week vacation and the recall of the importance of vigilance in aseptic technique. In this case, that was the attributable cause.

[Slide.]

In another case, an operator reached over open vials to remove a fallen vial on the line with gloved hands. This was observed and it was a common practice. This was considered to be the cause of the failure. Poor personnel flow has also been named in media-fill and sterility-failure investigations.

Poor aseptic connections; I just gave an example but we have seen that many times just this year. Poor sanitization procedures deficient or poorly executed; I have never seen more cases of that than in the last year. Construction in another room of the same floor of a facility caused increased airborne contamination. This has

happened a number of times. It is well-established in bioaerosol and other textbooks including the Macular Textbook of Aerosols showing that when there are construction facilities, mold can be widely dispersed in the facility and make it to places you would never expect it to make it.

In this case, a Bacillus was the contaminating organism. There is a specific species that made it all the way down the lengthy hallway through the aseptic-processing facility airlock--that hallway was uncontrolled because it is part of the office environment, et cetera--through the aseptic-processing facility air lock--now, you are in aseptic facility--into other clean rooms, into the aseptic-processing room, finally to the aseptic-processing line to the critical zone and into the product, all the way across the facility where construction was taking place.

There have been a number of sterility failures in a several-week period with this isolate in the product that coincided with the construction. The environmental monitoring showed an atypical trend of this organism and the firm concluded migration of spores from the area under

construction was, in fact, the root cause of the sterility failures.

[Slide.]

Another case, a new line was put together, installed. An HVAC was installed. The line was signed off as qualified, the HVAC systems, signed off as qualified by everybody involved with the validation and qualification report. But, to prove out that this process actually was in control, they did what firms do when they have major changes, as again recommended by PDA and FDA, they did a media fill. The media fill demonstrated inadequate HEPA seal and, over 90 percent of the vials in the batch were contaminated.

Velocity through HEPA filters. It has happened a couple of times in the last few years. I will tell you one quick story. In the case detailed on this slide, the firm had replaced a fan and installed the wires with reverse polarity so the fan ran backward and counteracted the other fans in the HVAC unit.

This problem was not detected by facility monitoring systems including a probe that was monitoring pressure drop across the filters and there was no check of velocity at the time to

confirm that the installation went well because a like-for-like change was not considered to be significant in the change-control procedures.

The firm ran for three months under these conditions. When they ran a media fill, they found eleven contaminated units in about 18,000 vials. They attributed the failure to velocity problem.

Finally, there are a number of cases where we have seen mechanical failures of filling tanks, main-pump failure, cooling system, leaks at joints or pin holes. All of these have been named in field alerts and in media-fill and sterility-failure investigations.

[Slide.]

With this background, we have worked to update our Aseptic Processing Guidance to address persistent areas of cGMP deficiency. Clarifying basic cGMP expectations will be beneficial to all of us in promoting uniform interpretation of a number of big-ticket issues that are unnecessarily murky. This advisory committee meeting provides FDA with an excellent opportunity to receive feedback on our aseptic-processing concept paper on these five important topics; sterilization options, aseptic-processing-design evaluation and

contamination prevention, media fills, environmental monitoring and personnel issues.

[Slide.]

I will close, in the last couple of slides, with just some specifics on the contemporary cGMP philosophies behind our concept paper. One of the main objectives was to recognize the advantages of new technology, automation and facility improvements. For instance, the compound acknowledges benefits of isolator technology by stating that isolators appear to offer and advantage over classical aseptic processing including fewer opportunities for microbial contamination during processing.

So we are noting the tangible improvement afforded by isolator systems as well as acknowledging the lower gowning requirements, lower clean-room classifications and the ability to campaign, which is a departure from the old twenty-four-hour turnaround manufacturing paradigm.

We also emphasize the need for a well-conceived design. For example, we discuss the use of air locks to provide better aseptic-processing-facility control. While stating that air locks are useful in multiple places, the

only place where we advise that an airlock should be installed is at the entrance to the aseptic-processing facility that directly interfaces with the unclassified plan area.

We use this example as we believe it presented the clearest risk to assuring predictability of clean-room air quality. We liberalized some old standards including velocity. We state that velocity parameters established for each processing line should be justified and appropriate to maintain laminarity and air quality within the defined space.

We have relegated the old 90-feet-per-minute number to a footnote and acknowledged that it is often used. The design section of the concept paper stresses modern principles of reducing direct personnel involvement in aseptic operation through use of barriers and increased automation, moving personnel further and further away from the product.

As an example, the BFS Section notes that blow-field-seal operations are highly automated and require reduced human intervention. In order to increase latitude for new technologies, we have loosened up the language in other places, also.

This acknowledges that there may be a prevailing standard that should be, at the minimum, used for many of the applications, but there are also alternatives that are prominent.

One of the ways that we are assuring latitude is through liberal use of qualifying phrases such as "where appropriate," "where necessary," in some cases, "as necessary," "generally," "normally." As a means of comparing the '87 guidance to the concept paper, we did a search and found thirteen uses of such latitude phrases in the '87 guidance. We are now using fifty-three such qualifying phrases in the concept paper for latitude.

[Slide.]

We have been listening to comments from industry throughout our revision of the Aseptic Processing Guidance and it has impacted on the content of the concept paper you have before you today.

I hope I have provided a useful briefing this morning on some of the scientific and practical underpinnings behind our current thinking and risk-based philosophies that we believe are instrumental in preparing a revised guidance that

will be most useful to the industry and FDA.

At the end of the day, agreement on targeted cGMP systems to detect trends before product contamination occurs will achieve the goal that is shared by all of us, a higher confidence in sterile drug quality.

Thanks for your attention and we look forward to your comments.

DR. LEE: Thank you very much. Would you like to take one or two questions?

Any questions for Rick? If not, thank you.

Next on the agency is David Hussong. David spoke to this committee before and he is going to remind us about microbiology.

Microbiology Review Perspective

DR. HUSSONG: Good morning. Thank you for the opportunity to describe the review role in the regulation of sterile products.

[Slide.]

The regulatory oversight of drug manufacturing and marketing is done by multiple organizations at FDA each looking at different aspects of the product and process. Regulatory review of drug application is done by specialized

review scientists at the Centers. Review groups in the Center for Drug Evaluation are aligned according to scientific discipline.

Since sterile drug products are unique by their microbiological quality attribute of sterility, applications for sterile products are sent to the microbiologists for specialized review.

[Slide.]

During drug development in the investigational new drug, or IND, phase, products are reviewed to establish safety goals and minimize patient risk. Manufacturing process development is then monitored during the IND and data are generated on processing experiences.

By the time drug applications are submitted, manufacturing process experience has been gained. The product specification tests and acceptance criteria and process requirements are available, then, for regulatory review. The reviewer evaluates whether the manufacturer's process and controls are appropriate and whether the process controls answer the appropriate questions to assure process control.

The entire manufacturing process, its controls, the manufacturing facility need to be

appropriate for each specific product to be marketed.

[Slide.]

New drugs and generic drugs undergo product-quality microbiology review at the Center for Drugs. The microbiological reviewers evaluate the sterilization processes and their validation, test methods and acceptance criteria. According to the specific conditions of each product and process. [The text of part of this slide was not recorded.] Sterility is an absolute concept and it cannot be determined by any test.

Since there can be no absolute determination of sterility, then some risks must be accepted. Scientific evaluation can assess those risks related to each product and process.

[Slide.]

The guidance the reviewers used is provided in a 1994 document that was reprinted and is posted on the web. It defines what is to be submitted in application for drug products that will be marketed as sterile. The introduction to the 1994 Guidance states, "The efficacy of a given sterilization process for a specific drug product is evaluated on the basis of a series of protocols

and scientific experiences designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product."

Data derived from experiments and controlled procedures allow certain conclusions to be drawn about the probability of nonsterile product units sterility assurance level. Based on the scientific validity of the protocol and the methods as well as the scientific validity of the results and conclusions, the Agency concludes that efficacy of the sterilization process is validated.

The 1994 Guidance details the elements of validation experiments, allows latitude for new experimental methods and criteria and provides for approval of these following critical review by experienced and qualified scientists. That document does not, however, provide specific cutoff points, limits and levels. Those are usually determined by the firm based on their experience and the product they are making.

[Slide.]

In the Center for Drugs, currently thirteen microbiologists perform these reviews. Eleven hold doctorate degrees with dissertations in

microbiology. Among the microbiologists doing the new drug reviews, there is over 120 years experience in FDA and/or sterile product manufacturing.

These reviewers include experts in heat processes, filtration, test methods development, microbial kinetics, environmental microbiology and clinical microbiology. Each has experience in aseptic-processing method and the staff had experience in guidance development.

The microbiologists in the Office of Pharmaceutical Science have offered commentary to this document and look forward to developing a rationale and cohesive document that will allow FDA to speak with one voice and with meaning.

It is not certain what forum this concept paper will take, whether it would be better to have it address FDA's training or the regulated industry. In a recent publication, the most recent from the Journal of Pharmaceutical Science, two prominent authors describe problems which have occurred recently where investigators have demanded tests or, in the words of these authors, unnecessary and they also describe them as dangerous.

We all know that there is additional work to be done on this concept paper and, certainly, they highlight an area which needs to be addressed. They conclude their commentary by saying that we need to get industry and FDA into a meaningful dialogue. I agree.

Regardless of the ultimate form of this document, the OPS microbiologists remain willing and able to provide assistance to the development of the document.

Thank you.

DR. LEE: Thank you, David.

Questions for David? If not, we have two more. Russ Madsen from the Parenteral Drug Association.

Industry Perspective

MR. MADSEN: Thank you. I wish to thank the FDA, all of the various divisions of FDA and groups within FDA and the advisory committee for inviting me to speak here this morning about FDA's new preliminary concept paper on sterile drug products produced by aseptic processing.

[Slide.]

You should have not overheads or slides, but you should have now in your packets the paper

that was put together by the PDA Special Task Force. We, at PDA, know that it is very difficult to get documents as complicated as an aseptic-processing guidance to an approvable state. After all, we are in the business of writing technical monographs and reports and getting them approved by a diverse bunch of smart people with varying opinions.

Those of us in industry in academia also serve on policy-setting committees and fight these battles every day. Therefore, we greatly appreciate the persistence and the effort the Agency has shown in producing this preliminary concept paper.

Every time we publish a new PDA technical report, there are two criticisms. It is too specific and, guess what, it is not specific enough. We also appreciate the creativity the Agency has demonstrated in publishing this as a concept paper to further the dialogue among all interested parties.

We are seeking this dialogue and we believe that it is essential to get the best possible work product. We applaud the fact that FDA has chosen to make the paper public at this

time and we are excited about the next steps.

[Slide.]

PDA believes the concept paper provides guidance useful to pharmaceutical companies and FDA field investigators. The guidance should enable inspected firms to know what to expect during FDA inspections of their aseptic processing areas and eliminate observations based on hearsay, outdated guidance or expectations resulting from what other firms did to comply with arguably overzealous FDA 483 observations.

There is a desire on the part of most individuals and companies to understand the aseptic-processing requirements and to comply. It is important that the final version is very clear on what types of limits and requirements are absolute requirements and what are suggestions where firms have the ability to make good scientific judgments based on the specifics of an operation.

We appreciate that the document does have areas where the need for such judgment is respected. The concept paper supports the advantages of isolators relative to conventional manned aseptic processing. We believe this will

encourage the use of isolation technology by firms that, having lacked guidance, delayed its implementation. It also provides the needed framework for open dialogue with FDA.

Finally, the availability of new guidance should eliminate use by the field of draft guidance which is unavailable to the inspected firms.

[Slide.]

PDA's concerns are grouped into categories; best practices and cGMP, technical issues and unconventional terminology, scope and harmonization.

[Slide.]

Departures from current industry practices include media fills conducted in worst-case environmental conditions, environmental sampling of critical surfaces that are terminally sterilized, the fact that isolators do not normally employ unidirectional air flows or redundant HEPA filters and there was no evidence to support that isolators must be housed in classified areas.

Further, the document goes on to say media fill should be conducted under environmental conditions that simulate normal as well as worst-case conditions of production. We believe

media fills which already tend to be worst-case because of growth-promotion properties of the medium and the extra manipulation sometimes required should be conducted under environmental conditions representative of normal production.

The document says that the monitoring program should cover all production shifts and include air, floors, walls and equipment surfaces including the critical surfaces in contact with the product and container closures. PDA believes that critical surface monitoring is not advisable because these surfaces are sterilized using validated processes. Monitoring these surfaces provides little meaningful information.

If the results are positive, it could mean that the surface contained one or more microorganisms or that it was contaminated by the act of sampling, itself. Even if negative, the result may not be meaningful because of less than perfect recovery efficiency.

Unidirectional air flow is generally unnecessary in closed isolators and the use of redundant HEPA or ULPA filters is not common practice and is unnecessary.

Finally, with respect to the need to

locate an isolator in a Class 10,000 or Class 100,000 environment, PDA believes isolators should be located in controlled but unclassified areas.

[Slide.]

Successful aseptic processing relies on strict adherence to specific well-defined procedures and on accurate knowledge of the critical factors that could result in nonsterile product if not properly controlled. Correct and consistent use of terminology with the industry and by FDA is critical to success.

The section on air filtration indicates that hot-air sterilizer vents should be equipped with membrane filters. HEPA filters should be used for this purpose, PDA believes. The document says that particle counts in Class 100 areas should be taken normally, not more than one foot away from the work site. But the concept paper fails to define what the work site is leading to unnecessary ambiguity and inconsistent interpretation.

The document says that air locks should be installed between the aseptic-processing area entrance and the adjoining uncontrolled area. Other interfaces such as personnel entries or the juncture of aseptic-processing room and its

adjacent room are also appropriate locations for air locks.

Typically, PDA believes that modern aseptic-processing areas are not equipped with air locks between the aseptic filling room and other portions of the APA. Finally, the terms alert limit and action limit should be changed to alert level and action level. Limits, we believe, are applicable to specifications while levels apply to process monitoring.

Specification--that is, limits--relates to a direct measurement of product quality that is required to be met by an official monograph or filed application. Exceeding an alert or action level does not produce an out-of-specification result.

[Slide.]

While the concept paper provides guidance in many areas, two of the most important questions are not addressed; that is, regarding media fills, how many units should be filled and how many positives are allowable. Other questions which remain largely unanswered are can a media fill be an exact model of an aseptic-manufacturing process with predictive quality which can be challenged by

going to extremes or is a media fill merely a demonstration that a manufacturer can aseptically fill a predetermined number of units under a given predetermined set of conditions without introducing detectable contamination.

There is little guidance offered relative to performance of the remainder of the aseptic-processing area outside the critical zone. Many aseptic-processing operations have extensive areas that are either Class B 100 nonunidirectional or Class C, Class 10,000. This is where personnel are located. The document should include more detailed guidance in these areas, we believe.

CIP/SIP technology; that is clean-in-place, sterilize-in-place technology. Although widely used today in aseptic processing, it is not addressed in the document.

Finally, the concept paper fails to provide a systematic rational approach to aseptic process control and risk elimination. While buildings, personnel and components are discussed, there is no clear discussion about how the process should be set up and how the segregation of product and the environment should be accomplished at each step in the process.

[Slide.]

Commenting on the 1987 Guidance Document, PDA said, "The PDA believes that the guidelines should include those areas of aseptic processing which are most likely to affect product stability, quality; namely the aseptic manipulations made by specially trained personnel during product handling and assembly. The physical means to sterilization employed by the industry have been validated to deliver sterility assurance level much greater than those which can be achieved by conventional aseptic processing.

The body of technical literature available on the validation of sterilization processes is adequate and considerable and could simply be referenced by the guideline. We believe these comments apply today to the current concept paper. While the concept paper builds on the framework of the 1987 guideline, we believe it should be focused on aseptic processing; that is, the control and manipulation of sterile components, closures and containers and the control, monitoring and maintenance of the aseptic-processing environment.

Subjects such as endotoxin control, equipment qualification and sterility testing are

covered in the literature in great detail. If FDA believes better information about these subjects is needed, we believe separate guidance documents would be appropriate.

[Slide.]

Finally, it would be most helpful to know when the document is providing guidance, should, and when it is defining requirements, shall, as these terms are used most frequently in isodocuments. Table 1 and all references to room classifications refer to Federal Standard 209(e). EIST, assigned by the GSA as the preparing activity organization for Federal Standard 209(e) has recommended that International Standard ISO 14644-1 superseded Federal standard 209(e) which became obsolete November 29, 2001.

The document goes on to say, "Air in the immediate proximity is of acceptable particulate quality when it has a per-cubic-foot particle count of no more than 100 in size range of 0.5 micron enlarger, Class 100, when counted at representative locations normally not more than one foot away from the work site within the air flow and during filling and closing operations."

We believe this section needs to be

harmonized with EU requirements where sample size and limits are quite different. The document says that each individual sample result should be evaluated for its significance by comparing to the alert or action limits. Averaging results can mask unacceptable localized conditions. A result at the action limit urges attention to the approaching action conditions.

The EU approach, on the other hand, is that environmental monitoring results should be averaged.

[Slide.]

Our recommendation are that the concept paper be reviewed by some kind of a committee, either an ad hoc committee of FDA Headquarters or industry or, perhaps PQRI, to resolve issues. The committee then submits the revised document to the FDA for review and approval. Final draft is issued for public comment and the revised aseptic-processing guidance is finally issued.

PDA believes the document provides a good platform for a final draft guidance meeting the needs of FDA Headquarters, ORA and the regulated industry. In order to quickly develop a final guidance document, we recommend that the concept

paper be reviewed by an ad hoc committee consisting of FDA Headquarters and field personnel as well as industry aseptic-processing experts.

We believe that media fills are an important component in assuring aseptic-processing operations are under control. But, even when a media fill consists of filling more than 100,000 units over three consecutive shifts, a media fill cannot assure the sterility of the next or any other production lot. We need to break the mold and find a reasonable alternative to massive media fills.

One possible solution would be to replace process-simulation tests or media fills with aseptic-process assessments or process-simulation evaluations in which the media fill would consist of a specified number of units--for example, 10,000--with a normal and atypical interventions running under normal line conditions with a specified acceptance criteria--for example, not more than one positive.

The media fill would be but one part of the aseptic-process assessment which would also include evaluation and documentation of environmental controls, environmental monitoring

results, gowning procedures, employee training, room-pressure differentials, air-flow patterns and maintenance.

The overall evaluation would provide a high degree of assurance that normal aseptic-processing operations result in products with high levels of sterility assurance.

We look forward to working with FDA, industry and other professional associations to develop a world-class aseptic-processing guidance document.

Thank you.

DR. LEE: Thank you very much. Any immediate comments? Yes?

DR. MOYE: I wonder if you could help me differentiate your concern about action limits and action levels. Could you say that again, please?

MR. MADSEN: An action level, we believe, is typically used for something that is related to a process. It is not a firm specification, and exceeding a level merely indicates the fact that the process has drifted from its normal state or, for example, some action needs to be taken. A limit, on the other hand, we consider a firm specification. So exceeding a limit would cause a

failure of a product, for example.

Typically, a limit is something like the USP specification or some number filed in an NDA or other form of application.

DR. MOYE: So, then, is your concern that the paper is inappropriately focussed on limits when it should be focussed on levels?

MR. MADSEN: In some cases and, in other cases, we believe that the paper is not specific enough. It doesn't provide enough guidance to know where a firm needs to be in terms of its compliance stance.

DR. MOYE: The action that is taken when a limit is exceeded should be different than the action that is taken when a level is exceeded?

MR. MADSEN: Typically, when a limit is exceeded, it results in a failure of the product or rejection of the product.

DR. MOYE: Thank you.

DR. LEE: Thank you very much. Bear in mind that we need some volunteers to review this paper.

The final presentation for this morning is from Professor Berit Reinmuller at the Royal Institute of Technology in Stockholm, Sweden. She

will be talking about design, control and contamination.

Design, Control and Contamination

DR. REINMULLER: Good morning.

[Slide.]

This presentation, airborne contamination in clean rooms, design matters, is based on research by Professor Ljungqvist and myself at Royal Institute of Technology.

[Slide.]

Our research has shown that the contamination risk can be described by the impact vector. The impact vector is depending on the velocity and the concentration of contaminants. The numerical value of K is the number of particles passing a unit area for the first time. The area is placed perpendicular to the particle flow.

[Slide.]

In a unidirectional flow, the particle impact can be calculated. If we have a continuous point source of contamination in the unidirectional flow, the concentration and particle impact can be calculated with this equation. After proper simplification, we can see that it is proportional to velocity and concentration.

[Slide.]

Class 100 environments become contaminated and the contamination ends up in the product. Here is a cross section of a unidirectional-flow unit with side walls connected directly to the filter. How can contaminations in the room air be intrained into this zone.

We have openings here and a flat surface perpendicular to the flow. If the surface is wide enough, we will have a stagnation region and the shape of the stagnation regions will depend on the size of the side walls, or the size of the opening. It is possible for room air to be intrained into the stagnation regions where contaminations move in an unpredictable way.

This is of special importance if small vials are processed close to the working surface.

[Slide.]

Another case is shown in this cross section. It is a unidirectional flow unit where the side walls do not connect to the filter and the filter, the clean air, goes out here. If this opening is too small, then room air that is intrained into to clean zone can be dispersed all over the clean zone and can be stuck in the

stagnation region.

[Slide.]

If we don't have any side walls at all, we will have an ingress region here where clean air and room air are mixed. We still have the stagnation region along the table and this situation is very sensitive to movements, movements of people, transport of material, doors that open, could cause ingress of room air in the clean zone and increase the risk of contamination of the product.

[Slide.]

This air movement you cannot see but visualization is an aid to understand the air movements. Here we have a unidirectional vertical flow unit. But, close to the horizontal surface, you can see the flow is horizontal. It sweeps along the bottle and, downstream, the bottle will have a way where contaminants are accumulated.

[Slide.]

Sometimes, the equipment we use in the clean zone--here is a vertical unidirectional flow unit. We have a small stopper ball here. The air moves nicely here. But around and above the stopper ball, it is a stagnation region where

contaminants are kept and it is a long cleanup period. Visualization is an aid but it is not enough for evaluating the aseptic processes.

[Slide.]

The LR method, the method for limitation of risks or similar approaches are very useful when evaluating aseptic processes and single interventions. The method is based on visualization of air movements to identify stagnation regions. A challenge test where a particle counter is placed in the critical area and simultaneously particles are generated outside or along interventions.

A risk factor is calculated and the risk factor is the number of particles measured in the critical area divided by the number of particles in the challenge. When the risk factor is less than 0.01 percent, less than 10^{-4} during the challenge test, then there is no risk of airborne contamination during ordinary operation conditions.

[Slide.]

I'm sorry for the slides here, but this should be a unidirectional air flow. We have sterile bottles here and a cover should be placed on the bottles. This is to illustrate how to

evaluate single interventions. The particle counter is set up close to the bottle opening. Particles are generated along the operator's arm and we compare manual operations placing the stopper on the bottle or using a tool placing the cover on the bottle.

In manual handling, we have a number, about 1,000 particles counted close to the bottle, a risk factor of 10^{-3} and an identified risk situation. Using the tool, generating particles in the same way, measuring at the same place, we find fourteen particles here. So, by changing from manual to an operation working with a tool instead takes the risk situation away.

[Slide.]

A case study by comparing different feeding or accumulation tables, the filling lines are the same. Rotating a feeding table about this side, the particle sensor above the table, measured risk factor, 10^{-1}, very high and that it was a bad design was confirmed by media fills.

We had much, much more than 0.1 percent contamination. We had close to 10.

A straight feeding table, the filing line exactly the same, the same particle sensor location

above the table, the same generation of particles outside the accumulation table, and less than 10^{-4} particles. Few particles measured and the risk factor less than 10^{-4} and no risk, and the media fills were, in fact, zero on the same filling line.

[Slide.]

I hope you can recognize an ampule filling line. It is infed from the sterilizing tunnel. The vials go around, or ampules. They are filled and closed and go out of the filling room there. It is all covered with unidirectional flow.

We tested the efficiency of the barrier. This is the filling line again from the sterilizing tunnel, the accumulation table. And then the filling zone. There are different doors here, one here. We placed a particle-counter sensor in the filling zone and then, in different spots along the line, generated particles outside above the doors wherever there was a small opening and below the side walls.

We measured zero, zero, and suddenly, here, above this door, when particles were generated here, we found particle ingress of room air in this locations. When particles were generated here on the table where you push the

buttons, we could also trace an ingress of room air to this. So, zero everywhere but two locations, two potential ways of ingress of room air. This didn't show on the media fills.

[Slide.]

So, to use the LR method or a similar approach improves the microbiological risk assessment. It is not depending on collection and growth of viable particles. It identifies dispersion routes of airborne contamination and it gives easy and easy-to-understand results.

[Slide.]

The ISO Class 5 operational status can be maintained in different ways. You can have tailor-made side walls. You can have restricted access barriers. You can have everything closed up in isolators and sometimes you need vertical separators along filling lines to prevent air movements and transport of contaminants along filling lines.

[Slide.]

Risk situations within the unidirectional flow are when obstacles are placed, and often we do place obstacles in the unidirectional flow. If they are close to the border of the critical zone,

entrainment from room air can occur. Wakes and vortices are formed. Large horizontal tables, large surfaces, cause stagnation regions. If you are processing small vials, then this is a problem.

[Slide.]

If we look at what the ISO 14698 says about biocontamination control, it says that zones at risk should be monitored in a reproducible way and a formal system for risk assessment should be in place to control factors affecting microbiological quality of the product.

[Slide.]

So risk assessment of airborne contamination requires good knowledge about the clean-room performance. It requires knowledge about the process in detail and also knowledge about the airborne dispersion of particles. Particles with or without microorganisms are transported in exactly the same way.

[Slide.]

Some requirements on the filling equipment used in unidirectional-flow radials. The should be easy to clean and have an aerodynamic design, reliable mechanization in order to prevent unnecessary interventions, a certain ruggedness,

simple orientation and unscrambling. It should not be necessary to build a filling machine of 96 parts in the laminar flow, unidirectional flow.

If possible, it should have good ergonomics for the people working along the line.

[Slide.]

When risk assessment is performed in a proper way and the safety is measured and evaluated, then we can design safety into the process and the risk of contamination failures can be prevented.

[Slide.]

This is the most common contamination sourcing in clean rooms. But today's clean-room clothing, clean-room underwear, clean-room dresses, is much more efficient than it was twenty-five years ago.

[Slide.]

Aseptic production areas do not only consist of the filling room. There are the rooms around it. And we have flows between rooms, between openings. If we have constant pressure differences, then the pressure differences will cause a flow of air. For example, a sterilizing tunnel opening on a filling line and a pressure

difference of 15 Pascal means that you will have a velocity of 5 meters per second through the tunnel opening. That air must be provided by the unidirectional flow above. Otherwise, room air will be entrained into the sterilizing tunnel.

Small openings, an opening 20 centimeters in diameter, will give the same outflow, 5 meters per second if you have a 15 Pascal pressure difference, and a flow of about 4 cubic feet per second out of the room.

One comment about the door. When you open a door, you lose the overpressure.

[Slide.]

When there are temperature differences, there are air flows. At the autoclaves, we often have temperature differences when the autoclave opens. Lyophilizers and sometimes at doors, doors between, for example, the changing room and the filling room, there might be temperature differences. When the temperature differences are four degrees or more, then the 10 Pascal overpressure cannot prevent ingress of air from the dirtier area into the cleaner one.

[Slide.]

This illustrates the case with the hot

autoclave being opened. The hot air escapes here and room air is entrained here over the load. We have a 40 degree temperature difference, 40 degrees Kelvin. Then the opening of an autoclave, 1 by 1 meter, the flow in the autoclave and out of the autoclave is approximately 1 cubic meter per second.

[Slide.]

A decreasing temperature for the lyophilizer, if we have 25 degrees in the room, -2 degrees in the lyophilizer, it is a difference of 25 degrees, then air will come this way. The cold air, when the door is open, will flow out and be replaced by air this way. How much air do you need to compensate for this? It can be calculated and you can predict, calculate, how large a flow you need here to protect the lyophilizer and to transport contaminations away from men working in front of it. It can all be calculated.

[Slide.]

If the autoclave looks like this, a huge high opening and let's say that 25 degrees will take in almost 1 cubic meter per second here and 1 cubic meter per second out. Instead, if there is a pit opening 20 centimeters high and the same width,

1.6 meter, the flow will, instead, be 1 cubic foot per second. So the difference here in the opening size affects the volume of the flows.

[Slide.]

There is a need to assess the situations of airborne contamination in a scientific way and design certainly matters.

Thank you.

DR. LEE: Thank you very much. Are there any questions? If not, there is some food for thought. You have the concept paper in front of you. You have the background behind this concept paper. You heard the presentations that help you to analyze this paper and engage in some lively discussions after lunch.

So, if there are no other questions, I propose that we adjourn until 1 o'clock when we have the open public hearing. I think there are six individuals. You know exactly who you are, what your order is and how much time you have and I will be watching the time very closely.

Are there any remarks from the administrative side? If not, thank you very much and I will see you back at 1 o'clock.

[Whereupon, at 11:38 a.m., the proceedings

at

were recessed to be resumed at 1 o'clock p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:00 p.m.]

DR. LEE: The next item is the open public hearing. I have six individuals. Please excuse me if I pronounce your name incorrectly. Let me go by the first name. Maybe that is easier. Ken? Ken, you have five minutes.

Open Public Hearing

DR. MUHVICH: I recognize the importance of this concept paper and it is important for the FDA and the industry to get together and get some consensus now rather than later. However, I would like to focus on something that I think everyone is missing. If it is not the elephant, they are ignoring it anyway.

Aseptic technique in this industry is, sad to say, not very good. If the industry does their job and the FDA does their job, then that will provide a lot in the way of sterility assurance for the products that are being put out on the street. Because of the nature of cGMP these days and the quality of systems inspection and so forth, much time is spent by FDA investigators in conference rooms looking at stacks of investigations to see if people are doing a good job with that and little

time is spent watching filling operations to discover that aseptic technique is not what it should be.

I learned aseptic technique as a young corpsman in the Navy on a hospital ship in Viet Nam. If the aseptic technique--if I had the kind of aseptic technique then that people have in clean rooms nowadays, the OR nurse would have smacked me in the head and sent me away until I could come back again.

People always talk about retraining in this but there is no guidance in the industry--I just want to make the point the supervisors in clean rooms are not doing a good job at all. They are there. They observe people with breaches in aseptic technique and they do nothing about it.

Aseptic processing and aseptic technique have to be 100 percent every day. There can't be a day taken off or then you are going to have the types of things that Rick Friedman was talking about earlier.

I recognize the value of this guidance document but I think people need to refocus--I didn't hear anybody mention the word aseptic technique today and it is typically not mentioned

anywhere. But the key to aseptic processing is proper aseptic technique. There aren't any people that I see, or very few people, I should say, that really know what it is and how to teach it and it is a big problem for this industry, as I see it.

Thank you very much.

DR. LEE: Thank you, Ken.

Any questions for Ken? David Miner who actually was my bodyguard from the hotel to here this morning.

MR. MINER: Little did I know how exciting it was going to be walking over here from the hotel this morning. I am Dave Miner. I am with Lily and I am speaking on behalf of PhRMA and I am going to echo things you have heard several times already.

We do believe firmly that good science-based GMP guidance could provide important advantages for all stakeholders in this process, better assurance of quality products for consumers, companies less likely to make mistakes and allow FDA to focus on the truly gray areas and the areas where things are changing or need to change instead of things that should be common accepted standard practice.

In that light, we welcome the concept

paper and the release of the concept paper. We know that significant effort has gone into carrying it this far. New guidance is desperately needed in this particular area and it is a positive step to publish a draft.

As you heard a bit from Russ and I am sure there will be many other comments going forward, this draft needs significant improvement. But, folks; that's normal. That is where is should be. That is part of the process of getting the good guidance is putting something out there and having a dialogue around it and talking about it.

So we should feel very good that we have it out there. Hopefully, many of things, as Rick talked about this morning, that are already included there are positive steps. Some others are going to need adjustment, but that is part of the process.

Which brings me to the importance of process. I believe, really, to get good GMP guidance you have got to have good process. If you don't have a good process, number one, it will never get out. Number two, it has no chance of being timely. This is an area that is moving too fast for us to wait five to ten years to get

something out. By the time you get something out in five or ten years, it will have changed on you.

So good process is really critical going forward. I think that process is most likely to be rapid, effective and provide cost-efficient gains in product quality over time if it comes to an active dialogue with industry, academia and regulators all talking.

We, in industry, have long been criticized and criticized ourselves when people in discovery research took a compound and "threw it over the wall to development," or development took a product and threw it over the wall to manufacturing. A very valid criticism.

The same applies when you think about guidance. You really need to have folks talking to each other in real time to think through what are the best ways to do things.

So, in that light, we wonder, can the progression of the concept paper and the draft guidance to follow perhaps serve as a pilot for a better process. Can PQRIs serve as a key incubator for this better guidance. PQRI brings those key parties together. We would like to see PQRI tackling key aspects of aseptic processing among

the technical experts that need to be brought together.

Specifically, on the concept paper, I am not going to comment, with just one exception, and that is that the importance of the regulatory system, not just guidance but all aspects of the system, encouraging positive change. Take, for example, the use of isolators. There is general agreement that a well-designed isolator can provide significant improvement over conventional aseptic processing.

This is, in fact, reflected in the opening part of the concept paper and there is new section, Appendix 1, on isolators. However, when you think about the system, to date, the regulatory environment in the U.S. appears to actually have discouraged the introduction of isolators, if you look at the update of isolators in the U.S. as compared to the update in Europe.

So, we need to very careful and thoughtful about how we regulate so that we encourage good change.

Let me just pick out one example. It is a very small one, but just as an illustration of how we need to be careful. Line 1458 in the Appendix I

calls for a six-log reduction of BIs on the inner surfaces of isolators during their decontamination.

By contrast--this is the case of isolators where we should be having better protection--there is no such requirement for the less protective conventional aseptic processing environment. So you have moved to a more protective environment and you have added a new expectation. Why is that potentially a problem?

The cycle times that are required for vapor-phase hydrogen peroxide to get to that level of decontamination, maybe you have to increase to realize that. You might be confident that all the surface areas that you happen to have inside that isolator are going to get there which may cause your management to question the viability of the project and whether you should be going forward with it at all.

This one requirement, being a new requirement, has the potential, along with other things, to discourage what I think we all would agree, when it is done right, is good change. So we just raise that as a cautionary note about thinking through how this will encourage good change, which we all need.

So, to conclude, PhRMA applauds the release of the concept paper and we look forward to looking with the Agency as it drives forward to final guidance.

Thanks.

DR. LEE: Thank you. Questions for David?

DR. KIBBE: I have a couple of questions, since you are the industry and standing there smiling at me. We saw some recalls on that bar graph which interested me, that there was such a big dramatic jump. I know you can't answer why all those were recalled but, just out of curiosity within your own shop, when you have a batch failure, is it more often a sterility problem or more often something else.

MR. MINER: I am not sure I can answer that question off the top of my head, but one thing to think about is how many aspects, and Rick talked about this this morning--how many aspects do you have to control when you are talking about an aseptically processed product.

So if you think strictly in terms of the number of systems that you have to control and the potential for something to go wrong, your odds are greater just because of the number of things that

you are trying to control. I can't quote statistics off the top of my head.

Now, I would say, with regard to that recalls thing, I think it would be helpful to look behind that as you try to get to root-cause analysis for any problem that you run into, and understand what are the factors that are driving that, what led to the circumstances where you had those recalls and pull those out, each and every one that is significant in there.

DR. KIBBE: But you don't have any sense of--what I am really getting at is how often do we say, okay, we are not going to release this batch because we know that there is a problem or that we think there might be and we can't prove it one way or the other.

MR. MINER: Oh, that definitely happens. Without the appropriate documentation, you can't go forward and release the product against the risk of somebody questioning whether--even if you thought it was all right, if you don't have the documentation, you can't release that product.

DR. KIBBE: Thanks.

DR. LEE: Thank you.

The next person is Professor Ljungqvist

from Sweden.

PROFESSOR LJUNGQVIST: Good morning.

[Slide.]

A microscopic vortex in a clean room is a fact. What do you know about vortices? Well, they will accumulate contaminants.

[Slide.]

That has been proved as well in theory as in practice experimentally. Here you can see the theoretical equation and, if you are smart enough, you see the concentration accumulation.

[Slide.]

But that is not so easy, so I show a smoke filter instead. Every photo is taken with intervals of a couple of seconds. You can see that accumulation effect of the vortex. What you should be aware of, vortices will accumulate contaminants.

[Slide.]

Laminar air flow is cold in the draft but it should be unidirectional according to my opinion. Here you have laminar air flow when you see particles follow the stream line all the way. Here you have turbulent air flow when you have the small fluctuations around. Most Class A environment in the pharmaceutical industry has a

parallel flow like this. So the right wording which I use should be unidirectional air flow and skip laminar flow.

[Slide.]

If you have obstacles in unidirectional air flow, and it is a low velocity, it will, in the beginning be a smooth stream line, smooth air patterns. But if you increase the velocities, you first will get wake vortices and, after that, vortex streets. If you increase the velocity more, you will be a high range of turbulencies.

[Slide.]

Here we have a practical case. You have a filter fixture here. First, you get the wake vortices and then the vortex street. In this case, you also get irritational vortices. By the way, you can see a filter down here in the critical region of such a vortex.

You are discussing, in the draft, about the sweeping action. That means that this should take away these contaminants in this region, also. You also write in the draft that one should measure at this level and then you said "or" at this level. I think it is very important that you measure also velocities in those levels.

So, in Line 257, an "or" should be changed to "and" because you should measure as well up here as down here.

[Slide.]

Here, if we have a person in a unidirectional air flow--in this case, it is a horizontal unidirectional air flow. You see the smoke source here and it goes out very smoothly. The air goes like this passing the person. Everything is okay.

[Slide.]

What would happen if the person raises his hands and arms? Then you get a sudden change of the pattern. In some cases, that can be very dangerous for the product or the man.

[Slide.]

Here is a horizontal unidirectional air flow unit. Here we have the HEPA-filtered air and the main direction of the air movements is like that. Here we have the smoke source and you can see how the smoke goes from this region and out in the ambient air which is the intention, of course.

But even if you have some bottles here and you have the smoke source here, it will go, not out. It will go back because of the way it

vortices up to the critical region and then out.

[Slide.]

Still, we have a main air flow out like this and the smoke source here. But you move your hand like this and then the contaminants will follow from the person into the critical region.

[Slide.]

In this case, you have the vertical air flow and the machinery. The moving machinery will also give disturbances, wake vortices, et cetera, and you see the complex and rather difficult situation in this region.

[Slide.]

I would only like to say the part in the draft be Lines 272 to 282 stresses the importance of knowledge about personnel movements which I think is important that we can read it there.

I have five minutes. After having heard Dr. Reinmuller's and my presentation, you can understand, see immediately, of course, that this picture does not show good aseptic conditions, if you are trained, of course.

Thank you very much.

DR. LEE: Any questions?

MR. MUNSON: If you take your velocity

measurements down basically at work height or whatever where the vortexes are, how do you get accurate readings?

PROFESSOR LJUNGQVIST: First of all, you shall not have that vortex system. If you have it, you don't get accurate. But you should have smoke visualization telling you it is not accurate.

MR. MUNSON: Okay.

PROFESSOR LJUNGQVIST: But if you get a sweeping action, you should be able to measure that and get an actual value because, with the sweeping action, you have the main flow direction and that main flow direction is capable to be measured. But, of course, you also see it with your smoke visualization. But I think you shall do both.

MR. MUNSON: Right. It has just been my experience that when you get down that--it gets very, very hard to get good readings because of the direction of the air.

PROFESSOR LJUNGQVIST: You should look at it. If you take that away, no one--I know that persons in the Nordic countries, they put an "or" there. That means that we don't need to bother. I will have the "and" because they should bother with that region.

DR. LEE: Thank you very much.

Mr. Becker from Merck.

MR. BECKER: Good afternoon, everyone. My name is Martyn Becker and I am here representing Merck and Company. I would like thank you all for giving me the opportunity to put forward the views of Merck on the document that has been published now by FDA, and thank you very much for that.

The document does provide good basic philosophical guidance for aseptic processing. What I would like to just put before you are some opportunities for clarification which exist within the document.

We think that there are concepts that would be beneficial to enlarge including qualification of the scope of processes that are referred to in the paper, specifically enlargement upon guidance that is given in the document. I offer some examples; references to limited aspects of bulk processing. The document indicates that it only applies itself in a very limited fashion to bulk processing

So the important points of some of the thought processes are not references; for example, aseptic processing of bulk materials post final

sterilization and the use of true closed systems.

There is a section on isolators, but it doesn't reference the use of different types and specifications within the industry. The relevance of the guidance to classes of pharmaceutical products that are not required to be sterile according to filing or usage but are processed aseptically because of the nature of the product. I am referring to things like oral vaccines here.

It would be beneficial to make sure that the terminology used is consistent throughout the document so that concepts contained in the paper can be most effectively realized--one of the biggest examples is a reference to ISO 14644 that you have already seen--which do not appear to harmonize with what is now obsolete in terms of Federal Standard 209(e) and the references throughout the paper are in the Federal Standard terminology.

The industry hoped that there would be some kind of steps towards harmonization of area classifications with regard to the European Annex 1 classifications and ISO 14644, especially since it has been stated within the revision of the Annex I, the European Annex I, process that it is intended

to harmonize with ISO 14644 for a particular specification.

We fully support the use of a science-based approach for the areas with in the concept paper although there are a number of these areas which are unclear. There is some sort of confusion, I think, with the table on Page 3 in terms of area classifications which appear to simultaneously refer to a less than 3 CFU limit for Class 100 which is immediately, then, modified by the statement that there should be normally no contamination.

It is not clear what the reference to 1 in 1000 units is within the process-simulation section. It is not clear what this is meant to convey. It is agreed that the use of inappropriate statistics is not meaningful for simulation acceptance, but it should be acknowledged that what is essentially a sampling process, within that process, there should be some sort of defined mechanism to apply the sample to the whole population of the simulation.

Also, you could cite things like filter-integrity testing with regard to the intent or the expected criteria, specific examples being

the guidance's relevance to hydrophobic vent filters, or the requirement to test depyrogenation tunnel filters in in-use conditions, which could be a safety issue as these might be up to 300 degrees Celsius.

Process-simulation requirements focus upon the simulation of the actual process and yet the extremes of the temperature and humidity are required which is not representative of the process as carried out. There is also no indication of what worst-case environmental conditions actually means.

A very important point is container-closure integrity which is important with regard to the aseptic-process validation, but there is very little reference to it. If it is required that another guidance document be referred to, then we would recommend that it specifically be referred to in the back of the document.

Isolator-background classification requirements are also unclear for all isolator types since it might be inappropriate to apply environmental criteria for open manufacturing isolators as well as closed testing ones.

In summary, we acknowledge that regulatory

documents are not normally over-prescriptive but rely upon the use of good science to make sure that sound justifications exist for the rationales used. We would support additional editorial input to assure a consistent implementation and the interpretation of requirements. Also, we support the assurance of the guidance process by supporting effective training of field investigators that will eventually be responsible for implementation of this guidance when it becomes a guidance document.

Lastly, it is our opinion that for such a document of such fundamental importance to the aseptic-processing industry worldwide, an appropriate review periods, say 90 days, would be at least appropriate for its review and full comment.

We support the manufacturing-subcommittee incentive. It is very beneficial in view of the global regulatory environment worldwide.

Thank you very much.

DR. LEE: Thank you.

Any questions for Marty? Very clear. Thank you. Maurice Phelan?

MR. PHELAN: Thank you. My name is Maurice Phelan and I am here on behalf of Millipore

Corporation primarily to thank the FDA, all of the FDA participants, in producing this document and the members of the committee for what has been a long way to document, I believe.

In particular, we would like to thank you for the inclusions. From talking to some of my colleagues and some of our industry partners, the rider inside of that document which really sort of tells us that, for things like introductions of new technologies, there is clearly, from our point of view, the latitude to implement new technologies assuming that there has been appropriate validation conducted around those and that, to us, is very important given some of the programs which we have in place to help this industry in the area of aseptic processing.

We understand, by the way, truly understand, that filters are a very, very small part of an aseptic process. But, to Ken's point earlier, filters work very well. But, if they are not connected properly, if good aseptic technique is not used, they probably won't do as well as one might think, not the fault of the filter.

[Slide.]

Just one area which I believe we are going

to further comment on, and by the way, as an organization, and personally, we would be delighted to participate in any review processes that result from the decisions of the committee or this meeting--rapid-transfer technology is referred to on Page 37, aseptic processing and isolators.

We intend to put forward some data as well as a discussion on the fact that there is a clear differentiation between decontamination, transfer and the ability to sterile-transfer through an appropriate port using sterilization sources such as UV technology 254 and UV. That assumes, of course, that the appropriate, well-thought-out and demonstrated validation package associated with that sterilization source can pass along with it.

We are currently working on some data in that regard to support some of the comments that we are going to make, but we believe that technologies like this primarily benefit this industry in the area of removing personnel ingress, particularly in the sterile-isolator area.

[Slide.]

Moving on, briefly, to the filtration portion and, in fact, the filtration-efficacy portion of the concept brief, Page 21, there is a

discussion of porosity of filters and pore-size ratings. This is really a semantic issue but the statement where 0.2 micron are smaller, if that were literally processed, it would, in fact, rule out something like a 0.22 micron rated filter.

That is not really the issue so much as I think there is an opportunity to have a discussion around decoupling pore-size rating and sterilizing-grade efficiency and, potentially, to open a further discussion where we talk about sterilizing-grade filtration as a function of the validation studies that have been performed around the process and the individual filtration step and not the nominal rating of a filter.

To that end, we would be inputting and further commenting on methods for validation of filtration efficacy building on some of the technical reports that are being produced by the PDA along with and to the point of the gentleman who spoke before me from Merck and validation of integrity-test methods for hydrophobic vent and gas filters and, of course, liquid-sterilizing grade filtration.

Lastly, although the concept brief does allow for the discussion of endotoxin removal by

membranes, there are some technologies, membrane-based technologies, in particular charged membrane technologies, which will remove very, very efficiently endotoxin from liquid streams and, although there is a lot of latitude in this document, as Rick Friedman pointed out this morning with the fifty-three broader statements where the word "appropriate" is used and generally is used, it may well be worthwhile having a discussion around that during the comment phase.

That is really all that I would like to say this afternoon. Thank you very much and, again, we would be delighted to be involved in any type of further processes that will help put our expertise together with your expertise to produce a great document.

Thank you.

DR. LEE: Thank you very much.

The final presentation is by Dimitri.

MR. WIRCHANSKY: Good afternoon. My name is Dimitri Wirchansky.

[Slide.]

I am a pharmaceutical technology specialist for Jacobs Engineering in Conshohocken, Pennsylvania. I also happen to be the Isolation

Technology Interest Group leader for PDA. In the beginning of the year, PDA put out a survey for the use of isolators and we wanted to find out how the industry was using isolators.

[Slide.]

The results of this survey were presented at an Isolation Technology Conference by PDA April into May of this year. Rick Friedman asked me if I would come to discuss a couple of the results of that survey as it relates to the sterilization or, rather, the decontamination of the isolator background. Also, I have addressed a few comments to Appendix I dealing with isolators.

The survey was sent out. We got fifteen respondents. This slide shows the different applications of those respondents.

[Slide.]

I picked out the ones that I thought were most appropriate, that being sterility testing and manufacturing. We had fourteen respondents for sterility testing. Most people were doing sterility testing. One response was for some specialized testing.

[Slide.]

Of those respondents, two reported a

decontamination to a 3-lot reduction. Ten reported a six-log reduction and one reported a sub-cycle, 10^{-6}, which really went to 10^{-12}. Then there were some other comments around 10^{-6}. So, if you look at it percentagewise, you have about 14 percent on three-log reduction, 71 percent for six-log reduction and 7 percent for that double-kill cycle.

[Slide.]

This looks at aseptic manufacturing and the applications include formulation, low-speed filling, higher-speed filling and some other more specialized applications.

[Slide.]

In this case, one respondent reported a five-log reduction. Six reported a six-log reduction. Then there was another comment around a total deactivation of BIs, 10^{-6}, which I counted as a six-log reduction. Then we had one other application using a three-log reduction for wrapped presterilized components or tubs and these are probably the presterilized syringes. That was a three-log reduction.

So we have 11 percent for a five-log reduction, 78 percent for a six-log reduction and 11 percent with a three-log reduction for that

specific application. As I say, the idea behind this was just to get an understanding of how people were using the decontamination process in the isolators.

[Slide.]

The introduction to Appendix I; I think coming out and saying the well-designed positive-pressure barrier isolator is better than conventional aseptic processing, I thing that is a very good thing to say because I go out and I help people design and build pharmaceutical plants. Some clients will come to me and they will say, "Okay; we are going to build a new aseptic operation. I want to use isolation technology in this application," and so on.

Other clients will say, "I don't want to use isolation technology in this application," because, basically, they are afraid that if they make that decision, by the time they get their assets producing that they will have spent a lot of extra money and wasted a lot of time and they have a concern in that area.

I think that a statement like this at least shows that the Agency is trying to be supportive of this technology and help advance the

technology. We also have clients that aren't quite too sure whether they want to go towards the isolator or to go to some form of a modified conventional technology.

I have been working in aseptic manufacturing since '71, so I am kind of getting to be an old guy, but I haven't really seen anything that has made an impact in aseptic processing the way isolation technology has. So I think, as a leader of the Isolation Technology Interest Group, it is my goal to try to foster the advancement of this technology in good applications throughout the industry.

[Slide.]

These comments kind of refer to some specific items about the isolators. I didn't try to be all-inclusive but just to get a flavor for what I see for some of these things. Glove integrity; this is Section A.2. There are some strong comments. "With every use, gloves should be visually evaluated for any macroscopic physical defect." You can read the rest of what is up there.

This is true. If you have a noticeable tear, that is a problem. Where you get to have an

issue is like what if it is not noticeable. Then you may find it later or how do you deal with this. People that use isolators are concerned about this.

I think that the statement in the proposed regulations focusses very much on the gloves. That is important because gloves are important. But I think it should be part of a comprehensive operating and maintenance plan for the isolators. I think this plan should include measure to minimize the risks posed by the glove such as under-gloving or over-gloving.

Proper aseptic technique requires the use of a sterilized implement such as forceps or some other thing for the intervention to critical sites. Basically, you shouldn't be sticking your gloved hand, even though it is an isolator glove, into the aseptic part of the process.

During discussions at the Isolation Technology Interest Group, the users were very concerned about gloves. Different companies have developed different strategies, putting on gloves over the--the operator would put a sterilized glove over the hand that went into the glove. One company talked about how they sanitized the inside of that glove.

Of course, they decontaminated the outside of the glove as part of the decontamination cycle for the isolator. One company also talked about putting a glove over that glove sort of like to protect the isolator glove. So, the people that are using these things care about that and it is a concern for them.

I think it is a valid concern. I just think that it has to be looked at as part of the whole because, if somebody is doing a procedure to try to minimize the risk of the glove, that we should look at that as part of the whole procedure and not just say, "Oh, well; there is a hole in the glove. What does that mean?" Has that glove been tested afterwards? Has it been plated? Do we find counts there, those types of issues.

[Slide.]

This one describes air flow. I think we have had two people already discuss air flow quite a bit. Where it says, "In most sound designs, air showers over the critical zone once and systematically exhausted," this pretty much describes a unidirectional-flow isolator. Those typically find application in aseptic filling.

Turbulent-flow isolators also have

application, perhaps more in formulation with or without containment because sometimes we make aseptic products that are contained, especially on the formulation side, you may have a turbulent-flow isolator. So I think it depends on the application and what you are trying to accomplish.

[Slide.]

Clean-air classifications; 10,000 for Class 100,000, background for an isolator. From an operational standpoint, when somebody says Class 10,000 area to me, I translate that into a Grade B area with air locking and gowning and everything else. When somebody says, "Do you think it is a good idea for me to put an isolator in a Grade B area?" I say, "Boy, that is the worst of both worlds," because an isolator is as fairly complicated piece of equipment.

If you want to do an isolator right, it has to be integrated functionally with the operation. You have air systems to integrate. You have decontamination systems to integrate and then you have to interact with it through gloves or through RTPs and all this other kind of stuff.

If you put that in a Grade B area so somebody is in full aseptic, you are making it much

harder to do that. Then it is like why do you have an isolator. So I kind of think that is a design nightmare and I know, if I were the operator in that area, I don't think I would like that very much whereas, if the operator is more comfortable and can interact with the equipment, I think you stand a chance of getting a better result.

I didn't address those comments just to air classification because, in some cases, if somebody has an older-style isolator, there may be a reason why they have that in what they may call a 10,000 air class. But I think a Grade C or a Grade D area, that Class 100,000 should be adequate for a production isolator especially if you consider that sterility-test isolators have been operating with excellent results in controlled nonclassified areas.

[Slide.]

Section C.1 talks about RTPs. I think, if the RTP is properly maintained, it should not cause an increase in contamination. However, you may want to limit interactions for process reasons. Like it is a lot easier if you can put a big container that will take a shift's-worth.

[Slide.]

I would like to get to one more, the decontamination. This is a six-log reduction. It is Section D.2. I think it depends on the isolator and the equipment inside. If you have stopper bowls and tracks that cannot be sterilized without opening the isolator, then I think it is a prudent thing to go for a six-log reduction. However, if you have an isolator that is used for handling presterilized components, I think a three-log reduction is adequate. So I think it depends on the application.

If my time is up, that's fine. There is only one more anyway.

DR. LEE: Thank you very much for studying the document so carefully.

MR. WIRCHANSKY: I do want to thank you for inviting me because I think it is important. Aseptic processing is very important and the idea of revising the guidelines is a chance for everybody to normalize expectations and raise the level in the industry. I just hope that, through these interactions, the agency will consider both the theoretical goal of raising the standards and also the practical applications of what people have to do when they work in these areas.

Thank you very much.

DR. LEE: Is there a question?

DR. BURSTYN: I have one question for you relative to the data you showed with the large number of manufacturers who are using a 10^6 kill, especially in light of the recommendation in PDA Technical Report 34 that talked about a three-log reduction. Can you speculate how much of that is really due to the lack of guidance and if it is somewhat a self-fulfilling prophecy where people are speculating on the 10^6 level based on, perhaps, Agency Issues 483s, or what may be a perception of what is expected by the Agency and other regulatory authorities?

MR. WIRCHANSKY: I think there is that concern that the client companies, or the people that I talk to, they want to get their processes approved. So, if they think that if they go a certain way, that their approval will be delayed six months or a year, they will probably weigh that against the extra work to do what they think is needed to satisfy the Agency.

On the other hand, it depends on what is going on inside the isolator. I used the example of the stopper bowls and tracks because that is a

part that directly contacts a product-contact surface. That is why I used the word "prudent." I think it is prudent to decontaminate those parts to a 10^{-6}.

But then I used, on the other side, if you have presterilized components, then essentially the bioburden should approach 0, when you put them in an isolator and then you do a decontamination, you probably just take an extra cycle or just--you are overkilling to what level when you have something that was essentially sterilized in the first place.

That is kind of where I was coming from on that.

DR. LEE: Thank you very much.

That concludes the Open Public Hearing. The next agenda item is on Manufacturing Issues Discussion.

Manufacturing Issues Discussion

DR. LEE: I think the format is there will be four presentations.

MR. FAMULARE: We have the question-and-answer session, actually, of the discussants on the agenda.

DR. HUSSAIN: The plan is to have FDA folks come and state the questions and focus the

discussion on the questions we have posed.

MR. FAMULARE: The first person who will be discussing the issues would be Kris Evans on sterilization options, an FDA investigator.

MR. FRIEDMAN: The agenda was actually supposed to include a discussion from the expert guests for twenty minutes followed by, then, Kris Evans' presentation..

DR. HUSSAIN: Vince, what that was, we were hoping the invited guests that we have, before Kris comes in, to sort of focus the questions, we would like to hear from them, the invited guests on their specific issues.

DR. LEE: Does everybody have the agenda? There is a big gap. That is why I was puzzled. So we have twenty-five minutes for discussion and we don't have to necessarily have formal presentations, just discussion.

DR. HUSSAIN: In a sense, I think what we would like to hear from the experts we have invited is their views on the concept paper and the questions that we have posed. Since we have twenty-five minutes, we have more time and we can use that time for them.

DR. LEE: So now it is clear. Mr. Munson.

Discussants

MR. MUNSON: I think many of the concepts and the issues that have been brought up before are still relevant. I do concur that, in some areas of the document, there needs to be more definition. I think media fills is a very, very large part of that. People are going to want to know specifics, how many to fill.

The issue of interventions is an extremely complex issue right now where I have to take 50,000 units worth of interventions and cram them into a 10,000 unit media fill which now really starts to make it look like I am validating something other than what I do normally.

I think this is something where there needs to be some balance. As you read the guideline right now, I have to take a full batch-worth of interventions, both number and type of intervention, and put those into my media fill. If we go with the concept that I am trying to validate what I would apply to a product, now I have deviated even from that and I have got something that has twice the interventions, or three or four times the interventions per number of units that I am producing.

It has also caused everybody to kind of go into some of the very weirdest media-fill processes where I have got some people that fill a few units and then do nothing and then fill a few more, and then do nothing. Then you have got the other kind that I fill some units, then I fill water units, then I go back to filling media, then back to water.

There are all sorts of permutations that are out there. I think it is really getting quite confusing so I think this is something where the guideline I think needs to be a little more specific and maybe reevaluate what it is we are trying to do.

We are trying to show the media fill and the process simulation is basically supposed to say that the process that I am going to supply to the product is capable of rendering a sterile product which is the product and the intent of doing this. So I think the process should be that I am going to do the normal number of interventions.

The number of units filled I think should be--you can come up with some function of what the batch size is because some processes, such as blow-fill seal, batch sizes can be 3 to 500,000

units is a batch. To do 5,000 units, this means I run the machine for five, ten minutes and I am done.

So I think some practical aspect could be devised that would allow me, for those kinds of processes, to have a larger media fill that would be more representative but yet not still be overburdensome to the industry.

So that is one aspect. I think the area of environment monitoring is another one that could use quite a bit of maybe further explanations, especially in the area of alert action levels and what do I do in response to those, could use with a little bit more because that is also a very confusing part in the industry.

So there are a couple of areas where I think more specifics would really assist the industry even without becoming too prescriptive but just giving guidance on what is the expectation, what is it that FDA wants to see when they come in to a facility.

I spend an inordinate amount of time dealing with those kinds of topics. They are very significant. One thing I was very happy to see, at least in this concept paper, is the emphasis on

doing trend analysis as part of that investigation and determining whether I need to do an extensive investigation of an environmental excursion or whether I don't have to do very much.

DR. LEE: Excuse me.

MR. MUNSON: Yes?

DR. LEE: Let me focus the discussion a little bit more. I think I might want to get my electronic gavel back, if necessary. But I don't think I need to. First of all, I think we only have about twenty-five minutes and there are six panelists here. We would like to hear from everybody.

MR. MUNSON: Okay.

DR. LEE: My fault. I did not make things clear. Moreover, we would like to hear your thoughts on design, control and contamination at this point.

MR. FAMULARE: That's right. The way we focussed the afternoon discussion is that, at least in this first part of the discussion, we will talk about design control and contamination, particularly the talk of Berit Reinmuller. And then we will go to sterilization options, personnel, environmental monitoring and media fills

and then have the panel be able to discuss each one of those.

So there was a break from Berit Reinmuller and there was a little confusion there. But we would like to at least focus this first part of the discussion until Kris Evans comes up on the design, control and contamination.

So we have all that media-fill comment and we will get back to answer that when we get to that discussion with Brenda Uratani leading that off. So if we could get the group to focus on those, starting with the design, control and contamination.

DR. LEE: Please.

MS. LOWERY: In terms of design, control and contamination, I think that the presentations given so far, in terms of the controls that have to exist in the aseptic-processing area in the critical zone are very important. Most of these focus, I guess, like we talked about a little earlier this morning on personnel being the major source of contamination in a clean room.

Once contamination is identified, obviously it is a little easier to deal with, but, in looking at the way people interact in an aseptic

process makes a big difference between a product's sterility and nonsterility.

So, in looking at the design aspects, I think that it is extremely important to look at the positioning of personnel in the critical zone, how they interact, to have their interactions be very well and clearly defined in standard operating procedures such that everyone knows how to intervene in the aseptic process with sterile tools and implements, et cetera, so that air flow is not disrupted and there is not the potential, then, to deposit particulate, viable and nonviable, into the aseptic product.

So that is a big concern is that the training of personnel, et cetera, in these areas as it relates to design control is something that may need to be a little bit more focused.

In terms of general contamination issues, in the clean room itself, I think there are several routes of contamination ingress into the aseptic-processing area. Certainly the biggest one is probably personnel. The other one is bringing materials and equipment into the area that go through an airlock or a pass-through and don't go through an autoclave or a dry-heat oven.

The potential for contamination there is great and usually I think what happens there in that particular scenario is that there is not a big focus on surface disinfection of these parts with a sporicidal as they ingress into the area. It results in the spread of contamination from one part to the surface of another through the operator. So the operator is basically a vector of contamination.

So I think that is a focus that needs to be brought up in terms of looking at the potential for controlling contamination in a clean room.

MR. FAMULARE: Do you have any specific suggestions in that regard toward the guidance as it is written, towards the concept paper?

MS. LOWERY: The concept paper could probably be a little bit more strengthened in terms of the particular aspect of the controls of bringing equipment and materials in through an airlock or through a pass-through. I think that has to be a qualified process. I think you have to use qualified disinfectants that have been shown to be effective against the bioburden that typically might be on these items as they are brought in. Then, the process, itself, should be qualified so

that there is complete assurance that there is no contamination being brought in that way.

There are other areas as it relates to personnel, then, in terms of gowning and what kinds of requirements maybe the guidance document should be strengthened on in terms of looking at gowning and the potential for people to bring in contamination which is the other viable route.

DR. LEE: Did you have something to add?

MR. MUNSON: Yes. On a design issue, I think a lot of us are focussing on the aseptic core. There is a huge part of most factories that is outside the aseptic core and, again, this is where the material movement and personnel movement--I think this is one of the weaknesses in the guide is this interaction between these areas that either support the aseptic core or are in front of it.

These are like putting transition points in between places like warehousing and then I start to move materials and personnel into a "manufacturing" area of the plant, maybe compounding areas, things of this--these are non-sterile areas, but I think it is critical to set up, from a design of a facility, transition

points where I have to do this decontamination or I have to try and retard contamination coming in from uncontrolled areas into cleaner areas.

So, the plant should be designed to get cleaner and cleaner as I get closer and closer to my aseptic-processing areas. I think this is something where the guideline really doesn't even get into that part of the facility and how that can play because that is all part of the "contamination control" aspects that should be built into a sterile manufacturing facility.

DR. LEE: Thank you.

Don?

DR. BURSTYN: I will try to be brief to leave some time for Mike at the end, here. I think that it is very--I want to make two points. First of all, we need to figure out a way to allow a more rapid implementation of new technology. It is clear that many of us go back to older technology because we are used to it and the agency is used to is and it is very safe for us.

We do avoid new technology because none of us really want to be a pioneer, the first one out there, and risk the chance of our approvals being delayed. Just a second fast point I want to make

is that reading through the document and hearing some of the talks, it is obvious that there are many parameters within a conventional fill room, within an isolator, of whatever, that we can monitor.

We can look at air flows at various areas. We can do environmental monitoring and such like that and we can collect a lot of data. We need to make sure that, just because we can collect data, that should not be the reason we are doing it. We need to make sure that the data we are collecting absolutely has some meaning to us and that we can use that data in order to help us to improve the quality of our processes and to ensure that better-quality products are getting to the end users, the patients.

So just because we can measure something, we shouldn't. We need to go back and really think about what we are doing.

I will leave it at that.

DR. LEE: Anne Marie?

MS. DIXON: I want to make a few comments on design. I think part of the problem starts when you don't lay out a process and then you don't have the adequate space in order to move items

throughout the facility. So the first thing that should be done is to analyze the process flow and then build the clean room or the controlled environments to suit the process.

When you try to shoe-horn it in, it gets to be very, very difficult. So that is going to give you a lot of entrances and egress areas for personnel movement and for things that go on to the areas. These are going to need multiple levels of control. Just adding a locker room two buildings over and having people tromp around through the outside in order to get over to the aseptic filling room doesn't work.

Yet, those are some of the things that people do every day. The same is true with bringing things off of trucks and then going through a passive airlock or passive pass-through and then assume it gets decontaminated.

So, having multiple stages of facilities, multiple egress and ingress points I think would be, in addition to the process flow would be very beneficial.

But then, when you get into the inside facility, I think we are having problems with things like smoke studies and trying to qualify

design. Smoke studies, certainly, in a passive situation, are much different than a dynamic condition which the two speakers earlier have shown us. But, not only that, the type of smoke could be a serious issue.

There are many smokes that are used today that are carcinogenic in nature and I think it is important for the Agency to understand that, that we just don't want smoke. We don't want a contamination thrown in the clean room just because we are trying to prove laminarity or unidirectional flow. But we want good science applied and want to actually see the movement of equipment, see the movement of people, and see the fact that the clean room can sweep items away.

That points back to having good filtration. Filtration is something that is very expensive today. Many firms, in their effort in order to cut back on costs, and "think green," are talking about reducing the velocities in the clean room, turning the clean room off at night and then going back to active condition in the next day.

This does seriously detrimental effects on a clean room. People are failing to go back to some of the original work that was done back in the

'70's and the '80's and the '90's by other industries in this clean-room field which have proven how you move particles, how you control particles, what happens to microbial during shut-down times, what happens when you reactivate fans.

So I think this whole science of the system and the design has got to be looked at very carefully. Otherwise, all the monitoring and all the training is going to be to no avail.

MR. FAMULARE: Again, do you have specific areas where you think the guidance needs to be beefed up in this area or changed?

MS. DIXON: I think it might be beneficial for the reader to have some references, in not just beefed up in some areas. I think we have got to address multiple use of airlocks. We have got to say something about using an active versus a passive unit. I think we have to say something about HEPA filters and making sure that these HEPA filters are tested with the appropriate standards by giving references.

We need to go back and reference some of the original work done by some of the aerospace people, some of the NASA people right here at

Goddard, which have proven what happens to clean rooms when they wind up being turned off at night and reactivated during the day. So the user can go back and look at this.

I think some enhancements on egress and ingress and some enhancements on references would be very helpful.

DR. LEE: Jeanne?

DR. MOLDENHAUER: I concur as far as this ingress/egress. I also support Sandy's comments about needing more guidance for validation of pass-through as this tunnel's disinfection and that as well. I am also concerned about just some of the things that are put in the guidance document; for example drains, and that drains are bad in clean rooms.

That is great, except that I have a lot of processes that are very moist in nature, compounding, washing componentry. If I don't have drains, then I have standing water in clean rooms which is not really a good thing. So I think we need to go back and look at that. I agree that it also needs more references.

DR. LEE: Mike?

DR. KORCZYNSKI: I sent my FDA colleagues

five pages of comments on the document so I am not going to reiterate those comments. I just wanted to play off some of the comments I heard today and maybe indicate some areas for inclusion in the concept paper.

One thing, for the sake of maybe providing some information to the panel, in some cases, I disagreed slightly with some of the speakers.

DR. LEE: Let us focus on design, control and contamination for now.

DR. KORCZYNSKI: Frankly, this is difficult to do, just given that direction in a moment. I would like to be able to just cite a few comments that I think are going to be beneficial to us. In this case, it was cited that aseptic individuals, perhaps, need better training and maybe the industry is derelict in that regard.

Well, I think people, in general, have to remember the industry has come a long way in aseptic processing. Along those lines, people receive yearly GMP training. People have to be validated in gowning. The industry, in many cases, has actual limits of 1 to 2 counts. It is getting to a point where basically the total process has basically improved.

If there is an area for potential improvement, if we look out in the next ten years, I would say that maybe would should consider a certified aseptic operator-training program, an aseptic certified program, for people who operate in manufacturing areas.

That could be developed by industrial associations in concert with the FDA and maybe an oversight could be the university that issues the certificate. But I think that that would give us some level of standardization among all operators regardless of whether they are with a small firm or large firm.

The other issue I found relative to the document, a key one. It is just like many of my colleagues said. I found it wanting in terms of not saying anything about the action levels relative to media fills. To those that are unacquainted, a media fill is a way of replicating the process and giving you some feeling that you have validated the process.

It is not the total answer but it is a pretty good answer. Of course, there has been an arbitration through this through the years. Many people classically have been using a 10 percent

mathematical approach. I think where the industry has improved is that, in my own experience, there seems to be a target level of 0 out of 3,000.

As a matter of fact, people have moved that up to wanting to see no positives out of units 3,000 to 6,000. Companies feel uncomfortable when then get one to three positives out of about 6 to 9,000 units. I think everyone feels uncomfortable in an initial validation if you have a hiccup in three replicate runs, whether that be one positive or three. That is inadequate. You have to go back until chronologically or sequentially you have three good runs.

So I think the document needs to address something along those lines. The other place where I found it wanting is what about the clinical fills. What about operations that are filling small clinical units, 500 to 1,000 units, basically? When do you conduct a media fill there? I would say that the isodocument on aseptic filling has a section that should be considered and reviewed.

Relative to this discussion on limits and levels, I think that that can be variable. I am frankly a proponent of limits because, in many

cases, many companies put their environmental counts in their specifications because it becomes part of their work-order procedures as well.

Basically, I think that one item I asked for inclusion in the document and it will appear stringent on the part of some of my industrial colleagues, but I think there should be a management review. When you have a number of counts that exceed your limits or levels in the Class 100 area, there should be some arbitration as to whether you are going to release that product or not, because now we are holding these environmental counts to be absolute rather than a trending analysis type of an approach.

So that was a suggestion.

I am going to answer one gentleman's question about sterility testing, the amount of positive units and all that we saw on the chart. I would say that, in my opinion, I don't think those were all reflective of sterility-testing failures because we know the industry has improved in sterility testing because many companies are now using isolators rather than the testing room to test the product.

As a matter of fact, one failure in the

initial test means that product is gone.

Just the other comment relative to barrier isolators, maybe what we could include in the document. There was discussion of these classical technologies versus barrier isolators. However, there is a hybrid and that hybrid is the conventional filling line where one may put a plexiglass cabinet around it. One may put curtains around that, so it is not truly and enclosed isolator but it prevents manual intervention during the filling of the product and, surprisingly--not surprisingly; in many cases, those data are excellent in that environment.

So that, in summary, is it.

DR. LEE: Okay; very well. What I have heard is the writers of this draft concept paper would like to have some specifics which I don't think is forthcoming, per se. But you hear the sentiment.

MR. ELTERMAN: One of the things I wanted to add to the design and controls is one of the things we did wrestle with, what was going to be included as part of the scope of the document. To answer some of the questions related to the HVAC, we sort of have that on a parallel track as a

separate guidance document that we see coming out about the same time.

We weren't in a position to present it here but, again, some of the various aspects of that will be covered in a separate guidance document.

DR. LEE: The philosophy of this is to be as broad as possible, to cover as many bases as possible.

MR. ELTERMAN: When taking a look at scope of this, we realize that there are additional things that we needed to have built in which would be probably best for a separate guidance document. So there was a lot of crossover between what could have been included in the aseptic process guidance document and the HVAC document.

So we haven't finalized that yet to bring it forward, but there has been a lot of cross-talk to try to make sure that the two documents harmonize which may address some of the issues that we have heard today, at least with respect to the HVAC controls.

MR. MUNSON: I guess, just from a design aspect, though, one of the things would have been this harmonization on the ISO designations. I

guess the biggest push for that is the harmonization effort. One of the things that is not in the document is doing a conversion from European 209 and ISO because that has got to be one of the most confusing things the identify has been wresting with is doing that conversion, because the European designations have an inoperation and a static mode and it's okay, and which one are we referring to.

People mix those up. They are using Class B's as being equivalent to a Class 100 U.S. But, again, we are mixing those up. So I think the document, if you were going to go back and relook at it, would be to do the isodesignations throughout the document and then just have a really small table in the front that would do the conversions as to what that means in the old terms and in the current European system, so that everybody would be very, very clear on what you are talking about.

But moving the rest of the document into the ISO which is slated to be the harmonized classification system.

DR. LEE: Comments?

MR. ELTERMAN: Again, that was one of the

discussion points that we had as part of the committee, how far did we want to go in looking at ISO. Certainly, there are concepts that are compatible with our document. We just weren't, at this point, ready to look at ISO and sort of embrace that. So that is a separate discussion probably yet to come but I certainly appreciate your comments on that fact.

MR. MUNSON: I am only talking about the classification scheme. I am not saying that you have to endorse the entire document. FDA never endorsed 209 in its entirety, but just the classification as to what do I call what, I think, is the aspect that I am looking for right now. Whether you endorse the entire Part 1, Part 2; yes, you can do that at some other point

MR. ELTERMAN: We tried to make reference to it as part of the table but, in as much as that has caused some confusion, we will go back and look at that.

MS. DIXON: In that you are going to be writing a parallel design document, then I have two design questions for you. There are two comments that are in--one is in Section C. It is actually listed as Line 170 which, actually, exceeds some of

the current standards. I think the industry would like a clarification of what you mean by 0.05 inches water gauge from room to room, because currently most people are following what was written in 1987 and in between the critical and the noncritical, that's true and in between the noncritical and the ambient, that is true but most people practice cascade between that.

If we are looking at going to 0.05 inches water gauge from room to room, then some facilities are not going to be able to meet that criteria even though they been licensed using the cascade. So I think that is an area that will need the committee to go back and look at it for clarification.

The second point for clarification under design, if I could refer the committee over to the next page, Page 6, under Line 240, this is also a deviation from what the industry has seen in the replacement of a HEPA filter should there be a significant leak.

In general, FDA has embraced the IST document, recommended Practice 6.2 in its use of a percentage and a size limitation. PDA has since even quoted some of that in some of their documents. So my question, again, to the committee

is are we moving towards a change? Are we raising the bar? Was that your intent or is it just a matter of semantics.

MR. FAMULARE: We did discuss these areas quite a bit internally. I could look to one of the technical people that worked on it to maybe come to the microphone if they want to clarify these points.

DR. LEE: Are you looking for volunteers?

MR. FAMULARE: I think either Rick or Kris.

DR. LEE: While Kris is coming to the microphone, let me give you a preview about what is ahead. We have four other topics, sterilization options, personnel and environment monitoring and media fills to discuss. Is that right?

MR. FRIEDMAN: I am just reading on the spot, just to refresh my memory on exactly how it was stated. We used the concept that areas of different criticalities should generally--that is one of the places where we used the qualifying word--generally have a 0.05 positive differential pressure relative to areas of lower criticality. But the word generally was used there to allow for latitude for firms who want to use something like

0.03 or something like that so they don't have to keep stepping up each from one room to one room to one room.

We do want to see the progressive pressure cascade from the area of lowest criticality to the area of the highest criticality as a well-accepted facility-control concept. If there is a need for clarification in the guidance, we could go back and, as we prepare to issue draft guidance, we can, perhaps put the example of the aseptic-processing clean room and its adjacent lesser-classified room in there as the most prominent example, the way it was in the original '87 guidance.

There are other options available, also, that we could consider. But we think they were generally provided for those instances and that is why we put the word there.

DR. BURSTYN: I think, in a way, it kind of points out that we have to be exceedingly careful and very deliberate when we choose our precise wording in this because this is often open to interpretation. Not only is this, in effect, going to served as a guidance for industry, often these documents actually become manuals for inspectors when they are coming into your plant.

MR. FRIEDMAN: When you have the word "generally," the advantage of the firm is that they can throw back those words and quote them to FDA in a 483 response. That is one of the reasons it is a side effect or byproduct of this guidance document, but it is an advantage for firms that they can then quote this document and say, "Well, FDA says 'generally' in their guidance document."

Also, we have seen a number of firms that, in areas besides--and this is one of the reasons why we have changed the guidance relative to only giving on example in the original '87 guidance, or we plan to change it, because we have seen a number of firms that have had a progressive cascade between an area such as the unclassified corridor that leads often through an airlock into the aseptic-processing facility, the introduction to the aseptic-processing facility.

This is another area where 0.5 inches of water gauge is typically used. So this is what we were trying to reflect in this guidance. It was supposed to be, instead of giving one narrow example, as in the '87 guidance, we were giving more of a reflection of the current status of the pressure cascade used by the industry for

contamination control.

So, again, there are a number of ways to approach this but I also do take your comment on improving the precision of the words.

DR. BURSTYN: I appreciate your response but also please remember we would actually prefer not to get a 483 than to have a great response to it.

MR. FRIEDMAN: Good point.

DR. LEE: Very well. What I propose to do--we are going to take a break. We are going to take a fifteen-minute break ahead of schedule, and then we will come back here at 2:40 and continue from there.

[Break.]

DR. LEE: Let me remind everybody about what was the general intent of the agenda. There is a concept paper for all of us. I think the authors of the paper would like to hear from us whether or not the document, as written, is scientifically sound.

I have no idea what the intent of this document is going to be. I think it is a guidance of some sort. Also, we just heard earlier there would be parallel documents developing.

Before the break, I was just curious to know what roll would the committee, on the same side of this table, play. I don't want them to say that we are not involved and take off. Obviously, we would like them to participate, like the committee to participate. I would like you to listen carefully from the experts, and then advise our colleagues as to which way to go, tell them your preference of a specific document or something flexible, and whatever you think would be scientifically sound.

That is want I planned to say. Now, the next person on the agenda is Kris.

Sterilization Options

MR. EVANS: Good afternoon.

[Slide.]

I am Kris Evans. I am a field investigator with ORA located in Philadelphia. I was also on the committee to redraft this document. It is my pleasure this afternoon to talk to you a little bit about sterilization options available to the manufacturers of sterile products.

[Slide.]

The Agency recognizes there are options available. Really, there are two principles to,

terminal sterilization and aseptic processing. However, it is very important to emphasize that, in offering this document as a guidance to industry, we did not to intend to imply that aseptic processing could be used as a suitable alternative to terminal sterilization where feasible.

Indeed, and really especially in light of the Agency's initiative to science-based risk management, aseptic processing continues to be a sterilization option of last resort.

[Slide.]

In the concept paper, in the scope section, we have included two statements in this regard, the first one basically points out, "It is a well-accepted principle that sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible," and, further on in that paragraph, "If it is not possible to terminally sterilize adjunct processing steps to increase the levels of sterilization confidence should be considered."

[Slide.]

I just want to briefly review some of the science behind our position but, before I do that, there are a number of terms in the sterilization

science arena, and I just want to mention two to help facilitate this discussion.

The first one is PNSU. It is the probability an individual unit will be non-sterile after the application of a lethal agent. So when we say a PNSU of 1 in 10^6, that means the probability that a unit is nonsterile is 1 in a million.

The second term is F_o or the sterilization process equivalent time. It is the equivalent number of minutes as 121 degrees Celsius delivered to a unit by a sterilization process. So the term, an F_o equal to eight minutes is saying that a cycle delivered the equivalent microbial lethality of 8 minutes at 121 degrees.

Since cycles are not always run at 121 degrees and there is lethality accumulated during heating up and cooling down, this F_o term enables us to compare different cycles under standardized terms and the probability of the non-sterile unit concept allows us, since demonstration of sterilization is not an absolute but is talked of in terms of probability, we use this term.

Historically, a probability of a nonsterile unit of 1 in a million, or greater, has

been the threshold for sterility by terminal sterilization.

[Slide.]

To address the question of is this, indeed, happening in industry, do we have instances where firms are aseptically processing product where terminal sterilization is feasible, the Agency doesn't really have information on that. But a recent PDA Technical Report No. 36, which surveyed the industry, asked this specific question at your site; "Is aseptic processing used for products that could be terminally sterilized?" They defined the "could be terminally sterilized" as "capable of receiving an F_o greater than or equal to eight minutes in its current configuration."

[Slide.]

The response to that question showed that approximately one-third of the firms, indeed, have products that meet that criteria and, of those firms, the side bar to the side shows that 2 to 85 percent of their products are affected. So if, indeed, your firms are processing aseptically where terminal sterilization is feasible, that is happening with 2 to 85 percent of their products.

[Slide.]

Again, to address this scientifically, we are talking of sterilization in terms of the probability of a nonsterile unit. For terminal sterilization, we were able to design and qualify cycles to achieve, indeed, a probability of a nonsterile unit of greater than or equal to 1 in 10^6. Those processes generally only have this one critical step, at least from a sterility-assurance standpoint, of controlling the final or terminal-sterilization cycle.

DR. MOYE: That is one in 10^{-6}?

MR. EVANS: Did I say 1 in 10^{-6}?

DR. MOYE: No. It is a probability or not? Is it a probability?

MR. EVANS: There are two different ways to look at this. I have tried to standardize it and it does get confusing. We speak of the probability of the nonsterile unit greater than 1 in a million. So the probability that a unit is nonsterile would be 1 million or greater. There is a sterility assurance-level concept that goes to the negative inverses, but we don't want to do that today.

Aseptic processing, on the other hand, it

really is scientifically impossible to establish or determine or qualify the probability of nonsterile unit. So there is a fundamental scientific gap, and we will look at that, between the ability to scientifically demonstrate sterility.

As we have talked about, the process involves multiple steps that factor in to the ability to produce noncontaminated units.

[Slide.]

Just quickly, the contamination rate, and I put that in quotes because that is a different concept than probability of nonsterile unit, can be assessed with media fills. So you can look at the rate of contamination within a media fill but that is different from qualifying the probability of a nonsterile unit. So it is important not to confuse those two concepts.

[Slide.]

The PDA also asked another question, and they asked firms to estimate the probability of a nonsterile unit for their aseptic processes. What I have tried to show graphically here is that, if the red is the percentage of firms that can meet or exceed this probability of nonsterile unit and the yellow is the percentage of firms that can also

meet or exceed that PNSU--it is a little tough to read, but at 10^2, or 1 in 100 PNSU, pretty much both processes will meet or exceed that level.

Since terminal-sterilization cycles are qualified to really meet or exceed 10^6, that bar remains relatively constant. But as firms have estimated, their ability to meet probability of nonsterile units degrades fairly quickly and there is the gap, in essence, between the ability to produce sterile products aseptically versus terminally.

This is 10^5, that is a probability of nonsterile unit of 1 in 100,000. 35 percent of the firms estimate they can meet or exceed that.

Adjunct processing, as we have proposed, would, in essence, shift all of the red bars to the right a little bit and move a higher percentage of aseptic-processing firms closer to this 10^6 zone that we have historically defined as the threshold for sterile products.

How far it moves to the right is difficult to assess, but I think, intuitively, the concept of adding additional heat to improve the percentage of firms reaching the higher levels of assurance is pretty intuitive.

[Slide.]

Just briefly, this is the slide the Joe had on recalls. It is the same one, all in one color. But I want to point out two key points. The lack of sterility assurance is the number-one reason for drug recalls in the last five years, and nearly all of the drugs recalled due to a lack of sterility assurance in the last twenty years were produced via aseptic processing.

So I think recalls, albeit a somewhat indirect metric for sterility assurance, certainly the science, or looking at it from this perspective, shows there is a concern, a gap between aseptic processing and terminal sterilization.

[Slide.]

We briefly looked at the global scene, what are some of our counterparts doing around the world. EMEA, the European agency, has put out a decision tree on which sterilization option to take. They recommend, if possible, terminal sterilization in F's above greater or equal to 15 minute and, if that is not possible, a form of adjunct processing, F's above greater than or equal to 8 minutes and also a probability of a nonsterile

unit of 1 in a million. If that is not possible, the last resort would be aseptic processing.

This is formalized in a decision tree for products subjects subject to the regulation.

[Slide.]

While we have similar concepts, I just want to point out two notes that are in that document. They say basically if a choice is made not to utilized terminal sterilization, scientific explanation and justification should be provided in the dossier, so they are looking for written justification in the application for not pursuing terminal sterilization.

The second point is heat lability of the packaging material should not be, in itself, the sole criteria for choosing terminal sterilization. We haven't been that specific in our document. At this point, we recognize that this issue will require a kind of a multifaceted approach but the document with this subject matter would be remiss if we didn't really emphasize our point that terminal sterilization is the preferred route where feasible.

[Slide.]

In conclusion, we just have two questions

for the advisory committee and the panel of experts; should terminal sterilization be used when feasible and should adjunct processing be considered in order to increase confidence in aseptically produced products.

DR. LEE: Thank you.

Yes?

DR. BURSTYN: I would like to ask a question first. I was at a meeting yesterday where Kathy Zoon, who heads up CBER, made a point that there were no recalls within CBER due to concerns about sterility assurance. Most of the products have all--well, the majority of them within CBER--are actually produced by aseptic processing, which, to me, implies that most of those 50 numbers are coming out of CDER or CDER-regulated products.

Can you comment, or can you speculate on why there might be such a difference between CBER- and CDER-regulated products?

MR. EVANS: Let me just clarify. First of all, it is the number of recalls, and each recall could involve multiple lots, for a lack of sterility assurance. That doesn't necessarily mean there was a nonsterile product on the market. The recall is initiated just because of a lack of a

sterility assurance, but not necessarily the finding of contaminated product. It could be GMPs.

This is drugs. I am not sure what Dr. Zoon was referring to. I am aware of some recalls, and I don't know what time period, certainly in the CBER industry or arena due to a lack of sterility assurance, not necessarily contaminated product on the market but would have fallen within these criteria.

MR. FAMULARE: We could go back and look at that data, but I think we really need to focus on, in terms of what the concept paper has said on the choice of sterilization options and get the respective input on that. But it is data that we will certainly look at with Dr. Zoon.

MR. MUNSON: Just to start off, I do agree with the first question--

DR. MOLDENHAUER: I just had a question, still, on his presentation. Since you are giving us all that data about recalls, could you please tell me how many of those were confirmed nonsterile products?

MR. EVANS: No; short answer. Rick is raising his hand. The data came from the Center for Drugs and we broadly classify it lack of

sterility assurance.

MR. FRIEDMAN: We have found, through government laboratories such as CDC, FDA laboratories, the firms' own laboratories, competitors' laboratories, cases where nonsterile products were on the market. Sometimes, occasionally, it has been in response to infections in a couple of cases.

But the numbers are fairly small. In fact, there were three nonsterile products found on the market this past year--given that the sterility test has such insensitivity to even to find the needle in the haystack is, of course, of concern to us--that were found to be nonsterile on the market.

Other years, there has been one, there has been five, there have been ten. Some years, there have been zero that have actually found on the market. So nonsterilities actually found in the marketplace are very difficult to get the exact number of what actually might be out there.

I also did a check on Monday, and we have 120 complaints over the last five years in pharmacies, hospitals, et cetera, on the product--I am trying to remember the name of the defect category, but product nonsterility suspected, it is

called, something like that, microcontamination suspected. We had 120, approximately. I think I have the numbers, actually, in my folder, over the last five or six years.

So pharmacies seem to be finding the problems with the products more frequently than laboratories find them.

DR. LEE: Let's focus back on those questions and become available to answer any peripheral questions at the end. Anybody would like to offer should terminal sterilization be used when feasible?

DR. KORCZYNSKI: I would just like to briefly comment on the first one. I think most of us would agree yes. On the second issue, that becomes a little more problematic especially related to practical application in the industry. What I mean by that is if you do a screening process either in formulation and/or in your initial stability studies and the product doesn't tolerate an F_o of 6 to 8, it is not unlikely, but it is highly unlikely, it is not going to tolerate a 2 to 3.

If it is not going to tolerate and F_o of 6 to 8, there is probably going to be some

degradation at 2 to 3 F_o and companies are not willing to take that chance. The other thing is that you might lower the possibility of degradation by using a lower temp for a longer time, and that has got a reverse effect at times of giving you more degradation than a peak high temperature

Then just from the implementation, you are talking maybe sterilizing--you have an aseptic-processing run of 100 to 500,000 units to aseptically process, then to move that over to a large SVP autoclave to sterilize for an F_o of 2 really becomes very inefficient and really difficult from an operational viewpoint.

All I am saying is, in theory, it is good. But, in practice, it is a little difficult to implement and it may not be possible.

DR. MOLDENHAUER: Along that same line, if you happen to use and you can handle an F° at 2, then I would have to wonder if you couldn't handle an F_o of 4 and have a 10^{-6} sterility assurance level with a combined biological indicator bioburden-based cycle which, for many products, you can by changing your temperatures and your parameters.

But I also am concerned about the costs to

us as industry in having to add heat processing steps and resubmit all those drugs with new stability studies and to support that as well.

MS. DIXON: I have a concern from a different angle and that is that, many times, terminally sterilized products receive a lot less attention. So I am hesitant to say go for terminal sterilization if you are just going to throw caution to the wind.

I think we still have to look at validation of processes. We still have to look at--all the safeguards have got to be in place. Just to run something through an autoclave or nuke it to death and then sell it to the public, I think, is the wrong approach. I think that we owe it to the public to make sure that we give them a safe drug but a drug that actually meets the component specifications for which it was designed.

DR. LEE: So we, once again, come back to science, common sense and the public health.

Kris, good job. Please sit down.

MR. EVANS: Thank you.

MR. MUNSON: As I have already said, the terminal sterilization, when feasible, I think just makes good sense. The second one is going to take

more work to define, again, what kind of heat treatment. The other thing is, when FDA tried this before, and we tried this in 1991, one of the main things that everybody fell into the trap was they said, "Okay, aseptic processing is 10^3. I give another 10^3, that is 10^6." They are not additive. You cannot add them, but that was something that everybody instantly went off and started doing because one is a contamination rate and one is a probability and you can't add them together.

So we have to do this kind of cautiously, and what are we going to define as an adjunct. If I won't stand heat, do I have to go to radiation? If it won't do radiation, do I go to pulse light? When do I quit all the adjunct processes that possibly are available out there.

DR. LEE: Let's come back to that later.

MR. MUNSON: It is just something that you would really have to think about a little bit on the adjunct.

DR. LEE: Thank you.

MR. EVANS: Just briefly, if I can comment on that, we are not asking to do additive sterility assurance but we are kind of appealing to the science of it. If firms, by their own admission,

are failing to meet that same threshold of 10^{-6}, or 10^{6} probability, adjunct processing of some form will, as I said, shift those bars to the right and they will move a higher percentage of firms to a higher degree of sterility assurance.

At what cost and what tradeoff, I think that was the question we wanted to pose, does the science and the experience that we have seen justify the additional work and cost of proposing this.

MR. MUNSON: But to get back to what Mike brought up as the practicality of it is you may have to accept not even an F_o type treatment. You may be looking at, "If I can heat it up to 80 degrees C for a short period of time, which means I might be able to do this with microwave tunnels or something like that that makes it also somewhat practical from a processing viewpoint, in which case I won't kill spores but I can take care of the vegetatives which, if we are looking at people as being my primary supply of microorganisms in my clean room, that would take care of that source of contamination."

So you may have to think of it kind of towards that light which would allow you to have

some practicality and may take care of the majority of the organisms that possibly could constitute the contamination.

DR. LEE: Thank you very much.

We will have the next person. I case you haven't noticed, Helen Winkle is here. Thank you for joining us.

I think we have gotten into the rhythm of the format. This must be Robert.

MR. SAUSVILLE: That's correct.

DR. LEE: What are you going to talk about; personnel?

MR. SAUSVILLE: I am talking about personnel.

Personnel

MR. SAUSVILLE: I am Robert Sausville with the Center for Biologics. It is a pleasure to be here today to speak with you and I hope to give you a brief overview on the personnel section of our concept paper. We were given five minutes each to speak. Kris used his five minutes and my five minutes, so it is going to be really brief.

We will do the best we can.

DR. LEE: So what is the short answer?

MR. SAUSVILLE: Yes.

[Slide.]

As you have heard during the day today, we employ the risk-based approach in the development of this concept paper. This extends to the section on personnel.

[Slide.]

It is commonly understood, obviously from the discussions we have had today, that personnel pose a significant risk to the aseptic filling environment which is arguably the most critical control point in the manufacture of these products. Organisms can be contributed either directly by individuals or they can hitch a ride with the individual into this critical environment less controlled areas.

[Slide.]

The bottom line is that poor aseptic technique combined with poor gowning technique at these critical control points results in reduced sterility assurance. Our concept paper suggests procedures to reduce these risks. Critical areas should have limited access. Operators should be appropriately gowned and practice good sanitization procedures both before entry and while they are performing the operations.

Personnel should be part of a sound monitoring program, which I will get back to in a few minutes and, as has been pointed out, the training of personnel is very important. A sound training program addresses key issues such as clean-room operating procedures, gowning procedures and aseptic technique. Ken, are you listening?

Finally, personnel should be appropriately qualified by completion of a successful gowning-qualification procedure and involvement in a successful media fill.

[Slide.]

Again, as stated before, organisms can be introduced into aseptic products and components by direct contact with nonsterile surfaces such as operator gloves or entrainment of organisms in the laminar-flow air from compromised personnel, either from a couple of examples, exposed skin or shedding from the gowns.

In order to avoid these problems, our concept paper describes good aseptic techniques including contact of material with sterile instruments, do not disturb the laminar air flow with rapid movements, talking or obstructions and to move slowly and deliberately.

[Slide.]

Getting back to the monitor program, the monitoring of personnel is used to qualify individuals for aseptic processing, to reduce the risk to the products being filled, provides a snapshot in time of the conditions the product is exposed to during aseptic filling operations and provides an early warning of potential problems if excursions are discovered.

We hope that you agree with our assessment of the risk posed by the personnel in these most critical processing steps and look forward to your input on this section of the concept paper.

DR. LEE: Any questions?

MR. SAUSVILLE: I do not have any questions other than we hope that you agree that personnel pose a great risk in the aseptic-processing area.

DR. LEE: So would should use robots as much as possible.

MR. SAUSVILLE: But we can input if you have anything you would like us to add to this section. Hopefully, everybody has read the section already.

DR. KORCZYNSKI: Relative to personnel,

out in the field, there sometimes seems to be a little misunderstanding or dilemma in terms of what to do. Tables will cite the action levels for personnel gowned and operating in Class 100. Then there will be tables in terms of gloves and gowns if they are in a Class 10,000.

But, in most cases, people are sampled after they run the operation in a Class 10,000 area and they transition from a 100 through the 10,000 into a 10,000 gowning room and are then sampled. So some people have asked, "Gee; what data table do I follow, in that these individuals had a transition from these areas?"

I am not looking for an answer, but that is a question that is asked frequently.

MR. SAUSVILLE: If it is okay, I will give you an answer, or at least a feeling on my part. I think that we would like to see personnel monitored as they are exiting the clean room rather than when they are in the Class 10,000 area because we want to see the conditions that they are in and what they have been exposing the product to.

DR. KORCZYNSKI: What I guess I am describing, in many cases, you will have a Class 100 area and it may be a barrier or it may be some

type of an isolator, basically, and it is place within a Class 10,000 and still considered a clean room. But it is that transition.

MR. SAUSVILLE: I understand .

DR. KORCZYNSKI: Maybe we have to give some consideration to either describing that or maybe modifying the limits by one value. I don't know. I haven't thought through it.

MR. SAUSVILLE: That makes sense.

DR. LEE: Robert, you did a good job.

DR. KIBBE: I have got a couple of naive questions. Is there any contemplation or does anybody have any information about contamination potential during a work session with a clean environment?

MS. DIXON: It depends upon the barrier capability of the gown and the gowning components. One of the comments I was going to make is that I think we should stress in this document that we do have to look at the particle-barrier properties and the microbial-area properties of all the gowning elements.

In addition to that, I would hope that we would stress that we want to see street clothes go away from the gown rooms in order to reduce that

risk because certainly someone who enters the gown room wearing street clothing and then puts on a sterile gown is not going to stay at the same level as someone who has had multi-levels of controlled gowning before entering some of the pregowning areas.

The other comment is that it also depends upon the person's ability to gown. Doing this type of gowning technique is extremely difficult because one risks the fact of cross-contaminating the exterior of the gown as they put it on. So we do have to spend a lot of time looking at training and we have to spend a lot of time looking at qualifications to make sure that, when we qualify someone for gowning, we are actually picking out sites that would not only tell us their ability to gown but their ability to handle the gown without cross contaminating it.

DR. KIBBE: Has anybody looked at whether or not so many hours into the process you are more likely to have an incident which would contaminate the field?

MS. DIXON: That has been documented under several technical papers and it has been proven, both from a particular standpoint and a microbial

standpoint. But what we can say in general cases is that once the gown becomes moistened, the barrier capability of that gown is lessened greatly so that, should a person perspire in the gown, should a person get wet during sanitization, that barrier breaks down.

DR. KIBBE: But no one has come up with a guideline that says--

MS. DIXON: There is data showing that two hours in a face mask with talking degrades the face mask. Yes, sir; that is published and that has been published.

DR. KIBBE: Should that be in here?

MS. DIXON: It could be. It could be referenced in there. The face mask, the use of gloves, was published by the second AIDS Conference in Montreal showing a two-hour breakdown on latex gloves, the use of a garment of certain barriers, the anti-static barrier being that of the two- to three-hour barrier, a herring-bone barrier being only a 30-minute barrier, a laminated barrier being one of eight hours. That is all published data.

DR. KORCZYNSKI: I believe the concept document doesn't address temperature control and a suggestion would be made to include 65 to 68

because if one gowns up in this uniform and stays in there for any length of time in an uncontrolled temperature environment, it gets terrifically warm.

DR. LEE: I think we are getting into some very technical issues.

DR. KIBBE: I was just wondering has anybody looked at--I don't know how to describe it--at swabbing or sampling from your workers before they enter and after to compare whether there is--do you know what I am getting at?

MS. DIXON: The reason I am laughing is that we have seen where the clean-room people tend to come out of the clean room actually cleaner than they go in, which is rather ironic. But that tends to be the caliber of isopropyl alcohol they are using as opposed to the clean-room condition.

So, yes; I think you could do that. The problem you have, though, is if you plate someone prior going in, you have to be able to remove that augur which is going to require some type of sanitization effort which is going to break down the barrier on the fabric and thereby imposing a high risk.

What you can do is to qualify gowning over a period of time and then plate people on exit and

get that relative data assuming you set up a protocol that doesn't allow them to drown themselves with a disinfectant prior to exiting.

MS. LOWERY: I also think, looking at monitoring personnel, immediately following the gowning process versus monitoring them at the conclusion of aseptic processing, we are trying to look at the impact of what has gone with their behavior, et cetera, over the aseptic-processing duration.

So, really, in all totality, the limits are existing for a firm for aseptic gowning qualification should, in fact, be tighter than the limits that you allow post-processing because, certainly, if you can't gown aseptically, there is really no hope for you to go into a clean room and present yourself in an aseptic manner.

So that is one recommendation that probably should go into the guidance that looks at the ability to have a tighter limit on gowning certification than post-processing.

One of the other things, in terms of limits of how long a person can stay in a gown in a clean room certainly also has a lot to do with their activity levels. If their activity levels

are restricted in terms of slow movement, et cetera, then possibly that amount of time is a little longer than people who are allowed to move quickly and to try and do a number of different jobs all in one time frame rather than being dedicated to the aseptic process. So that was another consideration.

I wanted to say just a couple more things real quickly about some of the things that I think should go into the guidance document. One of the big things we talked a little bit about, the controls that were around the facility prior to even going into the aseptic-processing area.

Personnel typically come to work and they change into a plant-dedicated uniform and plant-dedicated shoes. Now, if those are not truly dedicated, then the person can go outside and be exposed to the external environment and to the soil where many types of various microorganisms exist and track that basically back into the plant all around the entire area.

So, obviously, there has to be control over what the personnel are exposed once they have come to the work place and changed into their plant-dedicated clothing and shoes. So that is a

consideration.

The other thing, if you are going into an aseptic gowning room, it would be obviously beneficial to have the least amount of bioburden on a person's underclothing or clothing that they are going to wear underneath the gown, whether that be a plant uniform--ideally, it would be a sterile scrub or some type of way to minimize the personnel bioload because, as they go through the gowning process, it is, indeed, very difficult to come up with a sterile gown at the conclusion of gowning if you are not careful and if you have a high bioburden to start, the chances of contamination are a lot higher.

So I think that might be something to look at and, as Anne mentioned, gowns as good barriers is certainly something that needs to also be examined, whether they are maintained barriers over time. There should really be a useful life of gown materials because they are reprocessed. They are recleaned. They are resterilized. They are gamma-irradiated. There is a useful life and it is not necessarily just when the gown has rips or tears in it.

DR. LEE: The next topic is environment

monitoring.

MR. SAUSVILLE: Can I say one last thing. Jay, is the temperature and humidity control part of the HVAC document?

MR. ELTERMAN: I believe it is, but I would have to defer to Carolyn. She is shaking her head yes; it is part of that.

DR. LEE: I think this is teamwork in fine display. Rick?

MR. FRIEDMAN: Just one clarification on this sterility question complaint category. There are a number of different categories that FDA could use to indicate whether sterility problems exist in our complaint system called Drug Quality Reporting System. Sterility question complaints are just one of them. I think there is also contamination suspected, et cetera.

I checked the numbers and there were 114. Some of them are leaking containers, but they are--when I say pharmacies, they are hospital pharmacies using pharmaceutical-industry products or nurses, medical professionals that detect that there is a vial that has cloudiness in it or a vial that has cracks.

I have looked at the specific complaints

and I could give you a few examples if we had a little more time. But there are a number of different categories. There are 114 in this category over the last six years, about twenty a year, where a contamination is suspected on a pharmaceutical-industry product for a particular lot. It could have one to several units that were suspected, usually one.

So, one day, I will provide more thorough data at a PDA meeting or ISP meeting or some other forum.

Manufacturing Issues Discussion

Environment Monitoring

MR. FRIEDMAN: Atypical environment trends in a sterile facility can be detected through the establishment of a sound environmental monitoring program.

[Slide.]

Because microorganisms are invisible to the human eye, routes of contamination are not easily illuminated. Environmental monitoring provides critical and meaningful information on the quality of the aseptic-processing environment when a given batch is being manufactured and also can reveal environmental trends of the manufacturing

area.

An effective program will identify potential routes of contamination allowing for implementation of corrections before a product contamination occurs. The environmental-monitoring section of the concept paper discusses these basic environmental-monitoring principles and the need to have adequate systems for data trending and data interpretation.

The are many aspects of an aseptic operation that can directly or indirectly affect or disrupt the quality of the environment in which the sterile product elements are exposed. Here are some deficiencies that can cause or ultimately affect the Class 100 environment; poor air-flow patterns, contaminated equipment and material-flow patterns; personnel practices such as aseptic method breaches or poor clean-room behavior adjacent to the line; room-pressurization problems; disinfection-program deficiencies; inadequate procedures to address manufacturing anomalies that have occurred or have recurred.

All these have an environmental-monitoring piece. Environmental monitoring plays an integral role in each of these scenarios and the knowledge

of whether execution of procedures or control of such areas was successful is important in establishing confidence in the sterility of a given batch.

[Slide.]

I have discussed this chart earlier. It is used here just to highlight the environmental monitoring. The bottom right-hand corner, if you are facing it, it just one of the influential facets of a firm's assessment of their aseptic process.

[Slide.]

Risk-based environmental monitoring is about determining where the various sources of contamination may be and nipping those burgeoning contamination routes in the bud. Risk-based programs include meaningful measurement and consider the impact on or hazard to the product.

The concept document acknowledges that good scientific judgment comes into play when action-level departures occur and it is crucial. Our concept paper also notes that an environmental-monitoring program is most effective when, rather than using a grid-like approach to identifying sample locations throughout the aseptic

facility.

It, instead, includes carefully selected sampling locations. These locations and the associated frequency of sampling are based upon the location's relationship to the overall operation being performed.

You see our two quotes from the document. Very quickly, we note that, "Sampling, timing, frequency and location should be carefully selected based upon the relationship of the operation," and, "Locations posing the most microbiological risk to the product are a critical part of the program."

The issue that has often been debated is how much data must be obtained. One well-accepted risk-assessment concept is that, as more and better data is acquired, risk assessment improves. In contrast, a lack of data gives one minimal information to address whether a risk exists.

However, we acknowledge that environmental monitoring and aseptic manufacturing serves to provide a sampling of the environment that is adequate to give confidence that environment control existed on a given day of manufacture as well as over a longer term.

So this is why the concept paper places

most emphasis on locations in clean rooms and on equipment that pose the most microbiological risk. This is an example of an area that lends itself readily to the cGMP initiative to encourage risk-based approaches.

[Slide.]

Let's take a moment to compare the '87 Guideline to the 2002 Concept Paper on a few key topics. With respect to prescribing numbers in this guidance, we are aware that there are regulatory guidelines out there and industry documents that do, in fact, prescribe numbers for services

FDA has chosen not to do so and, instead, to allow firms to justify their surface monitoring limits on their own. We will then inspect and, in our other regulatory interactions, look at historical data and see if they are well-founded in the data at your facility and also considering the location that is being sampled.

With respect to critical surfaces, our original '87 Guidance says, "Endpoint surfaces which contact sterile drug product or sterilized container-closure surfaces should, of course, be sterile." The 2002 Concept Paper more succinctly

the states, "Critical surfaces which contact sterile products should be sterile."

We say it with no less conviction. We just say it more succinctly.

Establishing action limits; the original guidance stated air monitoring action levels without any qualification. The new guidance provides that latitude I was speaking of in my earlier presentation where different limits can be established "where justified by the nature of the operation." So we are not prescribing even air limits. We have provided that latitude, a new latitude, in this guidance, but they will have to be justified scientifically by data.

Identification; the original guidance says, "Routine identification of the recovered microorganisms should be done." Not every isolate needs to be identified to genus and species, but you should keep a valid database of the identity of organisms including in the ancillary areas.

In the 2002 Concept Paper, we say essentially the same thing. We stress ID in the aseptic-processing room as the highest product risks are generally present in that room. But then we say the ancillary areas can have an adequate

differentiation and at least frequent IDs to maintain the valid database. Again, keeping a valid database was implicit in the original guidance also.

[Slide.]

Let's look at a couple more issues on environmental monitoring. With respect to trending, we say that adequate systems should be in place to detect emerging or existing problems. By the time a trend is detected, that problem may already, perhaps, have product impact.

When a meaningful adverse trend is illuminated by the environmental data, the problem needs to be promptly addressed to prevent product contamination. This is in accord with all the industry and journal publications out there including PDA's Environmental Monitoring Technical Report No. 13, I believe it is, revised in 2001.

Interpretation; this is the area where scientific judgment becomes most prominent in devising the program that is risk-based. No statement is included in this guidance. Despite some concerns I have had at conferences over the years, FDA has not chosen to put any statement in its guidance that a critical zone positive, whether

it is a surface or it is an airborne count, is a surrogate sterility test.

We don't put it there for reasons that are very similar to what Mr. Madsen mentioned earlier. However, we do stress how important it is to look at the area that certainly would present the greatest point of risk in the operation if it became contaminated.

The point is that maintenance of the sterility of those surfaces throughout operation is imperative. That is one of the reasons why the industry has classically had the 24-hour turnaround, one of the reasons for sterilization of equipment. Just so long that you keep equipment sterile and run operations per the industry standards over the years.

So, instead, our expectation is that that data will be looked at as part of the holistic batch decision per 211.192. All data needs to be looked at, of course, associated with the batch prior to making a release decision for that batch.

So the cGMP expectation is for a holistic batch assessment with explanation of significance and impact of environmental or other deviations. As Mr. Madsen, again, said, these are deviations.

They are important deviations and they need to be looked at. They are not specifications. They are deviations from action levels or alert levels.

[Slide.]

So, to summarize our concept paper focuses on potential hazards to the product and discusses the need for a sound program. Otherwise, an emerging or existing contamination route will likely go undetected. We not that there should not be a grid approach but it should be risk-based. The nature of the operation determines its criticality.

Strategic collection of meaningful samples based on understanding of personnel and material flow through the facility should be elemental to the program. Detection of adverse environmental trends should be done through development of systems that detect the problem before there is a product contamination consequence.

Finally, responsive to identified should include a corrective action implemented where appropriate. That is how we say it in the environmental-monitoring section.

As you discuss environmental monitoring today, we are particularly interested in your input

on the following questions; do you agree with our stressing that the clean room should be monitored based on an understanding of how the process flows and should such points of risk be emphasized in the environmental-monitoring program.

What common sampling points in the aseptic processing and support clean rooms from your experience are most important to monitor as points of risk? Finally, regarding trends, are there certain elements of trending systems that provide the best mechanism for prompt detection of an existing or emerging problem? Also, what constitutes a long-term trend and do you typically see intra-day trends. These are a few questions that we are wondering about and we would like to hear your feedback.

Thanks a lot.

DR. LEE: Thank you.

Anyone?

MR. MUNSON: As far as to the first one, I do agree on doing it by a risk-based approach based on what the process is, how the product flows through, what the equipment looks like in the specific area to be monitored. So I think that is probably the way to do it.

Typically, for most lines, there is an in-feed. Again, this is where there is neither an accumulation table or something like that where I have the sterilized product either being put on the line or coming out of the tunnel, one or the other. Those are typically an area that is done.

The filling environment, obviously, where the solution is added to the containers. Stoppering area is kind of another one and, again, this may be dependent on equipment design on how far apart those two points are on the line.

Then, you have the out-feed and that is more for if it is a lyophilized product, you have an out-feed from the actual filling. Then, of course, you have got, if it is a lyophilized material, areas like in front of the lyo when it is open, being loaded, is another area that would have to be monitored.

So those are kind of typical areas that you would see for the majority of the lines. Obviously, that may have to get modified again based on what your lines actually does look like and how it operates. I think one thing that the document doesn't do is give a little more guidance maybe on when you say the number of samples or the

volume, say, like for air samples is what you would consider to be an appropriate volume, especially for the Class 100 area where I know some of the recommendations in the past have been.

In this area, since you are looking for such a very, very low number of organisms, if we even take the old NASA Guides back in 1969 of a tenth of an organism per cubit foot, that almost requires, then, you take a minimum of a 10 cubic-foot sample. It is just putting things in there like that.

I think the other area, while it talks about trends, one of the major issues here is what is a trend. Even the wording that is used kind of--if I probably polled ten people in here, we would come up with ten different definitions of what an adverse trend is.

I think you need to kind of either reduce that size or give a little more guidance on what you are looking at being an adverse trend. Is that consecutive failures? Is it number of failures within a time period? Is it something of that sort because, again, this is kind of the stumbling block.

Trending is one thing. Constituting what

is an adverse trend, at what point do I then have to react to this? It is a critical aspect for actually taking this to a more scientific-based process is defining trends. So I think this is something that might need further discussion, especially if we start going to allowing alerts and actions for basically all the areas of a clean room and then having to react to those because if I get an organism on one plate, my chances of finding out where that came from and what happened, if it is not part of a trend, is slim and none just be sheer chance.

So we don't want the industry chasing down a lot of ghosts and creating a lot of deviations that are going to have no outcome, no root cause, nothing to be done. So that is probably the most critical aspects as I see it.

DR. BURSTYN: I think the one thing I would like to add to what Terry said is that there are some sites that absolutely should not be monitored. Certainly, any product contact surfaces or surfaces that are actually in contact with sterile materials such as stoppers should certainly not be monitored before operations.

In all likelihood, it probably adds no

value to monitor those sites subsequent to operations.

MS. LOWERY: I would just like to talk a little bit about that comment and also about, I guess, looking at environment monitoring from a real risk-based perspective. I think we said that the routes of contamination into the clean room were likely by personnel bringing it in or by the lack of adequate surface disinfection of things coming in that don't come in through the sterilizers.

If you look at it from that perspective, when personnel, then, are in the clean room, I think it is a matter of the spread of contamination that may be associated with touch contamination transmitting the contamination from one aspect or surface onto another.

So I think one of the things that we need to look at is the aspect of touch contamination in a clean room. Where do people pick up contamination? Once it is in there, how is it maintained in there if you have a good disinfection program.

So if we look at the things that people always touch, door handles and telephones and carts

and shelves and pens and anything else, those are considered the vectors of contamination. Those would be, obviously, appropriate to be monitored.

We are looking at it for critical surfaces. One of the main things in terms of processing is equipment setup. Equipment setup is a major routine intervention that occurs with every batch where the equipment is brought in and is set up by one or more operators or a mechanic, and there is a lot of manipulation and connection that occurs from that perspective and there may or may not be sampling that is performed during a critical operation such as set up.

So it would seem that set up would be an appropriate time to gather airborne samples--certainly airborne samples and then, perhaps, the setup person after that person has completed operations.

I do think, in terms of critical control-point sampling, you certainly would not want to do that kind of sampling, for instance, stopper-bowl insides or filling needles. You would certainly not want to do that in advance of production.

However, if you are looking at the impact

over time of personnel intervening in an area, critical control-point sample with it being in closest proximity to the product can provide very meaningful information.

The last point I wanted to bring up was, again, the surface disinfection of items that come in. Those are routinely never on the environmental-monitoring program, along with things like particle counters and air samplers that are brought in. Those are never usually on the routine environmental-monitoring program either. So those, in fact, would be items that would be targeted for contamination potential.

DR. LEE: Any comments from the committee?

MS. DIXON: I think that we should also consider that particle counting serves a very strong purpose in clean rooms today because it is going to give us an immediate response is there is a problem where the micro data we are going to get several days later.

Looking at setting up routine monitoring, to have particle-counting sites in the same area as air microcides in the same general vicinity as surface sampling will give you very good picture of what is happening throughout the process and it

makes it much easier to go after identification of potential risk.

In addition to that, I would urge this committee to really strengthen the statement on "atypical" because we are seeing a lot of contamination that is not from clean rooms, it is not from people, and should not be there. I would, again, urge you to make sure that you strengthen that statement, that people not just look at numbers but they look at the type of microorganisms and where they could have come from.

MR. FRIEDMAN: If I could just interject for a moment and share one--the opinion of the committee that prepared the Environment Monitoring Technical Report No. 13 for PDA, it says, "One should take into consideration the extent of contact or exposure at each element that the manufacturing environment has with the product. Sites having greater opportunity for contributing bioburden into the product should be sampled and monitored. Product-contact sources may include compressed gasses, room air, manufacturing tools, critical surfaces, storage containers, conveyors, gloved hands, et cetera."

Examples of non-product-contact surfaces

include walls, floors, ceilings, et cetera. One should consider whether critical site monitoring would actually increase the probability of product contamination. It must be recognized that it may not always be practical to select a site at the most critical location because of this."

So that is a balanced discussion of it, but I think that that committee put together a balanced discussion of critical surfaces. I thought that might add to the discussion.

DR. MOLDENHAUER: I am a little concerned about the trending requirements, not because I don't think they are important. I think trending is really important. But I am concerned about the companies that don't have automated systems to do that. There is not a big selection of automated systems available and the ones that are available have very hefty price tags associated with them.

When you specify about daily, weekly, monthly, quarterly, monitoring and fifteen different ways you want to see reports, that is going to be extremely difficult for people doing manual systems. If you are going to do that, I think you need to have a phase-in period where they have an ability to get to a system that has that.

DR. KORCZYNSKI: Just a thought. If one was going to implement the risk-assessment system, I think it would be a good idea to have an SOP or a letter to file as to the rationale for the selection of those sites, getting prepared for a field inspection and the question being asked how or why to make that selection.

DR. LEE: Rick, do you have enough input to do the homework tonight?

MR. FRIEDMAN: I have nothing else to add to that. I think there were very good points made.

DR. LEE: So I would like to invite Brenda to the podium. Then we have some discussion and I would like to open it up and put everything in perspective.

Media Fills

DR. URATANI: Hi. I am Brenda Uratani, CDER Office of Compliance. Certainly, last is not least. I can see that there is great interest on the topic of process simulation of media fills.

[Slide.]

Will try to cover such an important topic in this five minutes of introduction before opening for discussion. In our concept paper, we have taken the risk-based approach in assessing the

adequacy of process simulation of media fill. This approach is scientifically based and I believe we are in substantial agreement with that of industry as evidenced in many publications.

There are a number of relevant PDA publications on the topic of process simulation of media fill. They include the PDA Technical Report No. 22 and the PDA Technical Report No. 24 as well as the points-to-consider for aseptic processing and a book on the microbiology in pharmaceutical manufacturing.

On the different issues concerning media fill or process simulation, as I see from those publications, I believe that FDA and industry are basically on the same page.

[Slide.]

Process simulation is of great value in assessing the capability of aseptic processing to produce a sterile drug product. While we agree with PDA that although a single media fill is a point-in-time analysis, that does not guarantee the sterility of all the future batches of product manufacturer on the same line. Successful, repeatable performance of the process-simulation studies over time provide a high degree of

assurance of the final product quality.

In designing a media-fill study, it is important to incorporate the same risk factor for contamination that occurs in production line and to consider the worst-case condition. I would like to clarify what we meant be the worst case.

By worst case, we don't mean that you artificially create the situation that will cause failure or go to such an extreme. I will give you some examples of what we meant by the worst-case conditions. They include a maximum number of personnel activities in the production run that should be simulated in the media-fill run because this number of personnel activities could have an impact on the quality of the aseptic environment.

Secondly, when you are using a matrix approach in qualifying a filling line, one should consider the type of containers or vials or the line speed that has the highest contamination risk.

Thirdly, one should also consider a sufficient number of representative interventions to be included in the media-fill run. It doesn't mean that you have to put all the interventions in one single media fill. It can be spread in a number of media fills so that you will know what is

the contamination risk.

[Slide.]

The level of sterility assurance is dependent on the aseptic techniques of the operator as well as the environment and process control. I think there is a broad agreement that value of this mediative study is only as good as is the true representation of the actual manufacturing process. So whichever media-fill approach is used, the firm should be able to justify the rationale of the media-fill design. So let's look at some of the critical factors for contamination in production that should be considered also in a media-fill study.

That includes duration and the size of the run, the line speed and all the personnel and manual manipulations.

[Slide.]

Although the most accurate simulation will be a full batch size and duration, we recognize that it may not be practical or necessary. In the concept paper, we stated that the duration of run should be sufficient to cover all manipulations that are normally performed in the actual processing, and we also said that the number of

units filled should be sufficient to reliably determine the contamination rate.

Our intention is trying not to be prescriptive. Our concept paper did not state, in most cases, a minimum number of media-fill vials that should be filled. Instead, we would like to allow flexibility and latitude. However, we hear the contrary, that you want some kind of specification on the number of vials.

So the bottom line is that the batch size of the media fill depends on the process, whether it is a large or small production-batch size. The line speed also is a factor. The duration of a media-fill run should be long enough to challenge the practical stresses of the process on the environment, as well as on the operator.

[Slide.]

Since it is well recognized that humans pose the greatest risk of contamination, let's focus, for a moment, on all the human aspects. Some of the human activities that can pose a risk to a sterile production include the start-up manipulation such as the weight check, aseptic assembly of the equipment, aseptic sampling collection during filling, aseptic additions, like

additions of sterile stoppers or sterile ingredients and other routine or non-routine interventions.

[Slide.]

Two other aspects of contamination risk that should be considered include the maximum number of personnel and the activities that will stress the production environment, the aseptic production environment, and the effect of shift changes and breaks.

[Slide.]

Finally, there has been a lot of discussion regarding the media-fill accountability and reconciliation and which are the counted in the assessment for the capability of aseptic processing. We came across many cases where a firm discards a large number of media-fill units arbitrarily. They are not specified in the SOP and they are not documented in the media-fill batch records.

We, therefore, feel that there is a need to address this issue and our concept paper provides guidance on the criteria where the removal of media-fill units are acceptable. Basically, the bottom line is that those interventions should

simulate what occurs in the commercial production run and they should be specified in the SOP in sufficient detail with regard to the type of intervention and the number of units removed.

The media-fill records should also document all the interventions performed and the number of units removed. We also note that many firms incubate these intervention units separately, even though they are not being counted as part of the media-fill run.

We agree with this approach because it provides the useful information for an actual production run to assess the risk of each type of intervention and to assess if the number of units removed is appropriate, whether they are too few or too many.

Currently, the general acceptance looks like it is one contaminated unit in 5,000. The interpretation of the limit to a number of allowable positive media-fill units should be carefully considered. Even though one or more contaminated units may be statistically allowed, it does not mean that it is acceptable for product release to contain a low level of contamination.

It is also the general consensus in

industry as seen in multiple PDA publications that the target for any process-simulation study should be zero contaminating units regardless of the size of the media-fill run and FDA agreed that target of zero contaminants can be achieved.

Since the assessment of the success of a media-fill run is based entirely on numbers and the target is zero positive regardless of run size, it is not difficult to see why every unit in the media fill would count and should be accounted for. So the removal of any units in the media fill should be fully justified.

In addition, FDA recognizes that there may be intermittent incidents of low contamination within the allowable limits but if it happens, one should look at the trend because it is important for the firm to investigate. They could be indicative of persistent problem and need to take corrective actions before major contamination occurs.

To summarize, I do believe that our current thinking on this issue is very much consistent with that of industry as judged from a number of publications. I would like to open for discussion--especially, I would like to ask for

your views on this topic and I would like also to solicit your opinions on media-fill units removed at set up because, at set up time, usually a large number of units are removed and this process is very manually intensive and much more complicated than most other intervention activities.

We are looking for a scientific justification why they should be included or not included as part of the media-fill evaluation.

Thank you.

DR. LEE: Thank you.

Any comments?

MR. MUNSON: Again, just to kind of go through maybe some of the shortcomings in the document, one of the things is set up is not specifically mentioned as being part of the media-fill process. It is not specifically that that is included as part of that, and I know, on occasion--or when it should be done or when you wouldn't allow it, like in a blow-field seal where it may be advantageous to put a media fill on the end of the run in which case I would then have to have a separate run that would specifically address the setup of the machinery or the equipment as kind of a separate issue.

Duration is one I am a little confused about. What is it we are saying there because I don't think the data is going to support that these rooms actually do get dirtier over time, because we do surface sampling and environmental monitoring is done throughout the process. I haven't seen that many companies that are really--again, if we have got adequate design, we don't have really design flaws or anything, that would indicate that these rooms are getting significantly dirtier over time.

The fatigue factor or operators; most companies I am seeing, operators are only in there for maybe two hours and then they go out for a break and then come back. So, if a company puts all that down, is that adequate justification for not having to do, like, a 30-hour media fill, if I don't have any indication that the rooms are getting dirtier or that people are in there so long that they are getting fatigued?

DR. URATANI: The bottom line is the firm should justify how they do it. There are many approaches. If your production run is, say, 30 hours, you don't have to fill all the 30 hours. You may be filling water in between or--there many different approaches and PDA has a publication that

lists the approaches, so the firm can choose whichever approach is appropriate for the situation.

As far as operator fatigue, I am not 100 percent sure when you say that you have never seen operator fatigue.

MR. MUNSON: It is just that operators tend not to stay in that long.

DR. URATANI: Is that true? Is that true that most aseptic operators in the filling room only stay there for a maximum of two hours?

MR. MUNSON: The maximum I have ever seen is four, and that is not that often. That is usually when they have had problems and the person needs to stay there to correct a problem. But people are not staying in these rooms for eight hours at a shot because it is very fatiguing due to the demanding nature of the work and everything such that you really don't want people in much longer than two hours. In many cases, they almost have to come out because you have to give them breaks.

DR. URATANI: But do think that this is uniform in all industries, that all firms only let their aseptic operators stay there for not more

than four hours?

MR. MUNSON: I think that is pretty much the norm, isn't it?.

DR. BURSTYN: I am not sure it is uniform four hours, but, certainly, I think all firms really recognize the fact that it is very uncomfortable to work in these rooms, being gowned in there. To be honest with you, our Environmental Health and Safety personnel don't allow this to happen because it is very difficult to have somebody standing up at a line for this amount of time.

So it really just doesn't happen, in my experience.

MR. FAMULARE: I think the focus, then, would be how to best express how to conduct a proper media fill in terms of how we expressed it in the concept paper. That is what we are really looking for feedback on.

MS. LOWERY: I think one of the things that maybe we could look at discussing is the concept of worst-case because, really, worst-case can be a lot of different things. It doesn't necessarily have to be the same set of circumstances for every single media fill.

For example, if you are looking for the impact of operator fatigue, maybe one worst-case media fill could be one that you follow on a production run and you retain those operators who have just worked all day on their shift, and they are fatigues. So maybe they would participate in the media fill at that point.

Another type of media fill could be one where you do capture set up like Terry--we were talking about, and maybe that is a different type of worst-case, things like--there are a lot of different scenarios that would constitute what is worst-case. So maybe looking at how to define what is worst-case, recognizing that it can be different for different fills.

MR. FAMULARE: I'm sorry. I think the term "worst case" really has to be looked at as we go back and look at the concept paper. Are we trying to define a case that is beyond what would ever be the operating parameters? I don't think that is the intention--as opposed to making sure that we capture most accurately all the various manipulations and intricacies that would enter into a media fill and be reflective of the firm's performance. So, definitely, the terminology and

so forth, we would appreciate the feedback on that terminology.

DR. LEE: Let me go back to Brenda. Brenda, you have specific questions for the committee? Right?

DR. URATANI: Yes.

DR. LEE: What are those questions.

DR. URATANI: Those questions are, we have set up criteria where media-fill units can be discarded because they are also discarded in a production run as part of the intervention. However, in a setup of a production run, when it is being simulated in the media fill, that process is much more manually intensive.

In a lot of cases, we see firms discard huge numbers of vials. So, is there any justification for those set-up units to be discarded or not to be counted as part of the media fill, even though they are not counted in a production run? That is the question.

MR. MUNSON: But I think you stated that very clearly in that this is--we are to simulate the process that occurs in commercial production. So, whether it is manual, it is automated, I have got a set procedure for how to manufacture a

product. If I clearly define in there what is rejected and what isn't in that process, then, when I do the media fill, I should be executing that same process.

If the batch record doesn't say, "Discard the first 50 vials off the line," then I really can't get rid of those because I haven't stated in commercial production, I am going to get rid of the first 50. So, again, we are back to we want to simulate what occurs in a commercial production run as far as what is defined.

Now, I have to define that even as far as if I do X intervention, you will clear ten vials on either side of that. That has all got to be clearly defined, and you said that. I agree with that concept.

DR. URATANI: But do we have any opinion to the contrary?

MR. MADSEN: Russ Madsen from PDA. We may be looking at two different kinds of media fills here. You have the media fills that you do when are commissioning a new facility or following a renovation or something like that, or you have got a new filling line, and you need to know a little bit about what is going on in that filling line.

You might want to run media fills to determine that and, in those cases, it might be helpful to incubate the set-up units to try to see where you have got a problem or if you have a problem.

I think that is different from media fills on long-running conventional aseptic processing lines where you already know that information. Those media fills should simulate the actual production processes as closely as possible. In those cases, it is probably appropriate to discard those set-up units.

So I think you have to look at the two types of media fills and the information you are trying to collect from both types.

DR. URATANI: I agree with you. I always think that whether you count the intervention units, whether they are set up during the production run, is always useful, at least at the beginning, to incubate them so that you can gain some information from that and you know that whatever is specified in your SOP, that you are discarding ten vials or 100 vials. That number of vials is justified.

MR. MUNSON: Again, that is almost like

having development runs to determine what those specs should be which is a little different than saying, "I am going to use these runs to determine my sterility assurance."

DR. URATANI: No. That's right.

MR. MUNSON: So we are talking different purposes and that should be clearly delineated when I set up the protocol for what I am going to do and that is where I should define what is this intent of this run, what am I trying to prove.

If I am trying to determine if I do this intervention and how many units to take out, that is one purpose. I may treat that different. I may take the vials off the line in a totally different manner because I am trying to look for specific cases here.

So I think most of us are trying to think of this as these are the routine media fills that we are using to show that we continue to be able to manufacture, in this facility, sterile products. So duration is a big factor of having to do these 30, 40, which says, on a blow-field-seal machine, I have got to do a three-day media fill, which starts to get really, really impractical and also to do these switchbacks back and forth between water,

media, water, media.

You are entering in a lot of other factors that you wouldn't normally have during production to do these kind of switch-outs.

DR. URATANI: Are you suggesting, in the concept paper, we want to address all kinds of situations, whether it is as high-speed fill, whether it is blow-field seal or Form Q seal?

MR. MUNSON: I think this is where the proposal here is not necessarily that the duration has to be for a full media fill. I think this is where some of the emphasis on the number of units to be done, and it basically says, if we put some sort of a minimum and then plus we add on to that some factor that takes into account the batch size, the maximum batch size, such that you start to get at least enough units to make an assessment.

So if I make a 3 or 4 or 500,000-unit batch, that may say, "Yes; I am going to have to fill 50,000, 60,000 units," or something, whatever comes up. This may be a discussion point for the exact numbers, but something that says, "Okay; you have got to fill 5,000 units minimum. If your batches are less than 5,000, you do the maximum batch size." But it is 5,000 plus 20 percent of

the maximum batch size in addition to that.

That is how we are going to factor in the huge batches. But it is not saying I have to run a three-day media fill. Then, during that course of action, I have got interventions. In some cases, you have said maximum number of interventions and then, in others, that you have to simulate interventions.

So maximum number; is that a maximum number for a three-day run? Or is that the maximum number for the number of units that I manufacture. Again, we are getting into clarification on that because, as it reads right now, it would be, "I have to do three days' worth of intervention on a 60,000 unit run."

DR. LEE: We are going to give Terry a break. Thank you, Terry.

I would like to open it up for a few more comments and then I would like to sum up the meeting.

MS. DIXON: I would like to ask the committee to comment on Lines No. 639 and 640. I really think that needs clarification because it states, in the document, that all personnel who enter the aseptic-processing area, including

technicians and maintenance personnel, should participate in a media fill at least once a year.

I think we need to clarify, does that participation have to occur before they are allowed to work in the facility or are we going to let them work in the facility and then, whenever the media fill comes along, they get to go in and participate. This is causing great confusion in industry and it really has to be--we need a position on this because media fills, in some plants, only occur every six months.

In other plants, they occur as a monthly event. So, with the turnover in personnel we are seeing in the industry, which is huge, the question is, how does a firm interpret this.

DR. LEE: Let me interject here. I think this is an important point. There is considerable variability from firm to firm. Therefore, I would like the committee to begin to think about what is our advice to the OPS as to how to approach this, through a risk-specific document, or should we have something which is very broad?

Bear in mind that it has been a number of years since this draft was done. Who knows whether we are going to wait another twenty-five years for

the revision.

So I would like to open this to the experts for their comments and then I would like to sum this up and bring everything to a close by asking my colleagues around the table about what their advice to the OPS is.

DR. HUSSAIN: I think a number of individuals also raised the question of PQRI. I am not sure I fully grasp that concept, what aspect are we talking about in if I can get somebody--

DR. LEE: To me, this is the beginning of a dialogue. Let's not try to accomplish everything today. I think we get a flavor about what this document is all about. I think this is a concept paper and I think we tend to look at this differently. I can sense that some might prefer this to be akin to--not to that extent, but to the Constitution, flexible, subject to interpretation, or something to be a cookbook-type.

I think, certainly, our colleagues on the other side had heard the comments. I think these comments were based on experience and, therefore, I am sure that they will take that into consideration. And I heard that there might be Version 1.1, Version 1.2, that sort of thing,

coming out.

So let's hear from the experts on this particular issue.

DR. BURSTYN: I think, to respond to the question, certainly it is valid to have an ordered approach where an individual may obviously--who hasn't participated in media fill and, as a consequence, perhaps, does not have the level of training, will not be allowed to perform critical operations over the line and such like that but, nonetheless, for auxiliary operations that take place that are activities that are completely distal to the operation, that they certainly could participate.

Obviously, we kind of view the ability of these folks to do some minor activities and observe as part of the training of these personnel. So, certainly, there has to be an allowance for that.

DR. LEE: Sandy?

MS. LOWERY: I was just going to say that I think that is a good approach to restrict their activities in terms of what they might be doing if they have not participated. But what a lot of companies, I think, have already done is they are looking at some sort of a personnel broth fill as

an initial qualification step because it is inconceivable that a company could just run a media fill for every single person that gets qualified to go into a clean room.

You might be running a lot of media fills in a particular time frame. So, in order to not do that, companies have decided, some companies have decided, to create a program for operator training that is an independent personnel qualification where it is taken off-line. It is still with media but it is more of an aseptic technique challenge consistent with the types of activities they would be performing during routine production.

The other good thing about that is if you put people into a media fill that are really not completely trained and there is a failure, then you have indicted your entire line because someone is not trained, which is not very smart. So it might be that taking it off-line is a better option and then just the next time that that person--the next time a media fill occurs, that person participate as well.

But, in the meantime, perhaps maybe they don't do as critical of operations, but that would be defined by the firm.

DR. LEE: Thank you.

DR. BURSTYN: If I could just make one more just general comment. This section on media fill is really directed towards aseptic filling of vials. But there are many of us within the industry who are doing aseptic manufacture of bulks where we do run media tests for aseptic simulations, but I think, in this section, and certainly within the rest of the document, that there needs to be some sort of comment, or some understanding that aseptic processing is used for operations other than filling operations.

DR. LEE: I would like to pose one question which I did not hear comment about. Maybe that was because I was falling asleep. One of the questions says, "Does this document encourage innovation in the aseptic-manufacturing arena?" I haven't heard any comments on this. Does anybody care to address that point?

DR. BURSTYN: I would love to address this one, to be honest with you.

DR. LEE: Bear in mind that we need to adjourn the meeting by 5:00.

DR. BURSTYN: No, no. I will be very brief. A lot of it goes toward--and I have alluded

to the fact that we need to make sure that we figure out a way to encourage people to use technologies that have the potential to add quality to the product. Certainly, isolators are one area.

We have heard from a number of folks that the update of isolator technology, which ultimately does what everybody is trying to do and that is to physically separate the operator from the product. The update of that technology in this country has not been very good. A lot of it is somewhat because of perceptions through various 483s, or meetings, or rumor or whatever that it is actually a very difficult technology to validate.

The standards for an isolator are much more rigorous than that for a conventional clean room. I think we certainly need to dispel that perception and do everything we can do to actually get people to use technologies such as isolators, and there are other technologies. There are the UVs and such like that.

Again, we have to stimulate people to do this rather than discourage them. I would hope that, within this document, or in general through other efforts of the Agency, that we make this a very active program.

DR. LEE: Yes?

DR. MOLDENHAUER: I would also like to see--there are numerous areas throughout the document that talk about specific media, specific culture methods, specific incubations. At bare minimum, I would like to see them put in some exceptions that allow for rapid micro systems because this document will be extremely detrimental to the already negative perception that people have that FDA will not support rapid microbiology.

DR. LEE: Other comments?

DR. KORCZYNSKI: Just reiterating, I think, what the others did. As I read through this, I didn't see it overly descriptive. I think that is good. I think we have to provide companies with the ability to use technical alternatives and, if they have the wherewithal and confidence to defend their alternative technical methods that they might be using.

So I wouldn't want to see this document become a road map, or a detailed road map.

MS. LOWERY: I agree with that in general, but I think there are instances where specifics are needed and they are actually wanted. Really, in terms of media fills, duration and yield are

certainly one aspect of it, acceptance criteria, and, because there is so much emphasis put on acceptance criteria, while the target, of course, is zero, what would be the acceptable number of units?

This is a big deal and it needs to be defined so that there is some sort of guidance that is available for industry.

DR. LEE: Let me now give the committee the benefit of some comment.

DR. KIBBE: I just have a question. Do you have, in here, and I have read it a couple of times but that's okay, I might have missed it, where the guidance covers a positive challenge to the system that you are putting in place and what that constitutes?

DR. URATANI: What do you mean by positive challenge?

DR. KIBBE: We are assuming the system will remove microbial contaminations. If we never challenge the system with the microbial contamination, how do we know it does and is there, in the normal workup of putting a system together, a microbial challenge to the system that is done--and it is not in this document; right?

DR. KORCZYNSKI: That's right. I think, from a practical application, most people don't want to go into their aseptic operation and seed it with microbes, with spore-formers and all, and see whether that influences the media-fill recovery rate.

But there are growth-promotion studies to show, indeed, your media supports growth but a very interesting study was used by the PDA and this concept was tested at the PDA where they have a training facility and they inoculated, purposely inoculated, stoppers, the bowl, parts of the line. They used increasing microbial counts. Russ is here. He can probably more accurately describe the results.

But it appeared there was sort of a break point at lower levels, 10-1, 10-2, 10-3 in terms of log numbers, you didn't see much. When you started getting into that 10-4, 10-5, 10-6 population, you started.

More recently, that is about the most recent data I have seen in that regard.

DR. KIBBE: So if I am a brand-new manufacturer and I am putting a brand-new line together, I still wouldn't even test it to see if

it worked with a positive challenge?

MR. MUNSON: You typically don't do that. You test the individual component of it off-line. In other words, like, for the air-filtration systems, you use particles that would--non viable particles that would simulate organisms or challenge it with the smallest sizes.

You do your disinfectants. You can challenge them in the lab, but taking known contaminants into a clean room is just not a good concept just for fear that you are not going to get them all out or something of that sort.

So, basically, you do a lot of this work off-line and then you are taking great care when you go back and then use them in your facilities just as disinfectant studies are done on each of the surface types.

So if you have got formica, stainless steel, a linoleum-type product on the floor, you are going to test that disinfectant on each one of those surfaces to make sure there are no interactions or neutralization of the disinfectants. A lot of these studies are done out in a lab outside of the clean room and are just part of the start-up process, but you really don't

take organisms in and challenge--

DR. KIBBE: When you are using a system for making the same product over and over again, you are assuming--maybe I am being a little--you are almost assuming that you start out with a sterile product and you are just doing this just to make sure.

MR. MUNSON: This is a capability study. It is saying that the process is capable of it. The ongoing--this is the emphasis on the environmental-monitoring program, that it has got to be complete and everything, and the trending is looking at how well you are maintaining all of these surfaces in your facility.

So it is pulling all of that information back together. I do the process simulation and that starts to bring in all the factors of people, machinery, air handlers, everything. But I am also doing environmental monitoring on a routine basis to make sure that I can demonstrate control of these.

So this is where all these other processes that we are doing and all this other monitoring, how that plays into that so that I don't have to do positives. I show that I don't have the buildups,

that I am not having any of the adverse trends that you have heard talked about quite a bit

DR. MOLDENHAUER: I think you would also off-line challenge the filters, themselves, and that is where you do a positive challenge with high levels of bacteria to understand exactly how much retention that bacterial filter has, and that is an off-line study. But I think that is really where the challenge that you are looking for comes--

DR. KIBBE: Okay; so you challenge there and you have a process in between each run where you know for sure that no matter what load showed up on your filters, you have cleaned it out and it doesn't stay in your system

DR. MOLDENHAUER: That's right.

DR. KIBBE: So there is no need to come back in later and rechallenge your system even with low levels; right? Is that what you are-

DR. MOLDENHAUER: Yes.

MS. LOWERY: The same thing for sterilization validation. You would do the same thing. You would challenge those loading patterns with highly resistant, thermally resistant, spores and then prove that they are gone.

Really, the only part of this that enters

the aseptic process that is really not sterile is the person, is the operator and everything they bring to the process, itself.

DR. KIBBE: The product has to be considered "nonsterile" when it starts.

MS. LOWERY: It is, but it is sterile by the time it is delivered to the aseptic process. It is presterilized prior to that, unless it is terminally sterilized.

DR. LEE: I think you may want to take Art on a field trip.

MS. LOWERY: But the clean room has been challenged and many people probably don't realize this, that there have been published studies on actually challenging clean rooms where the rooms have been seeded and then disinfectants have been applied, and the techniques have actually proven that, with the proper housekeeping techniques, you can do removal of surfaces.

So that challenge data has come out since the work that PDA has done. Where there work was really showing the challenge on the components, this work was showing the challenge on the ability to clean surfaces in a room.

DR. KORCZYNSKI: The fact of the matter is

there is very little hard data from a scientific viewpoint correlating the contamination in the environment to intrusion into the product during filling.

DR. LEE: Art's question is very intriguing. We never thought about doing this, but I think it is something worthy of thought.

I think there are four questions in the booklet that were posed to us. Let me try to answer on behalf of the committee and then the committee can tell me I am off-base, if that is the case.

Does the concept paper identify the most relevant topics for guidance development in the area of aseptic manufacturing? Based on what I heard, it is not perfect but I think it covers most of the territory. So I think this needs another iteration.

The B question, and then I am going to let you speak. The second question, is that document, the concept paper, grounded on science. I think it is. Is it sufficiently detailed to provide industry--it think that is where the problem lies. I think maybe my advice is that maybe you need to--I mean, just my opinion--as to you may want to

think about what you want this document to be.

I heard comments about there are places where it is too detailed and then there are places where it is not detailed. I think, perhaps, we need to think about whether or not you have enough detail. What additional considerations--I think that you may want to consult with the experts off-line and I would like to reemphasize that I would like to see some kind of a mechanism to encourage innovation, that, after all, the document has to be sufficiently flexible.

I think that we need to look forward into the future. I think that obviously the document, the guidance, ought to be appropriate for today but, since we are all busy, we should not want to be visited too often. So I guess the question is how far in advance should you look. This is something that is very hard for any aspect of science.

Then, the fourth question is to address each of these areas. I think that you get a flavor about what is coming through. So, all in all, then, I believe, from my perspective as a layman in this area, that I learned a great deal. I think the discomfort is not knowing what this document is

going to be used for.

But it seems to me that it might be useful, once the guidance takes further shape, that the inspectors, the investigators, however they are called, will be trained so that they will understand the conceptual basis for this guidance and therefore will know how to use common sense to respond to the situation in a specific facility.

I do hope that common sense is going to carry us, and with science, we should be okay. This is my perspective. I would just to now open this up for comments by my colleagues. I think Marv is ready to jump.

DR. MEYER: You really hit on one question that I had, what is the next step, what is the time frame, what is going to happen to the concept paper next.

MR. FAMULARE: This concept was issued preliminarily in terms of our issuing draft guidance, so the idea was to get as much input as we can before we put out the draft guidance which will also allow for public input. So, by having this session, I think we were fortunate to be able to get a good bit of input that could better formulate the paper.

There has been, as recognized by Dr. Lee and brought up by Russ Madsen and by PhRMA, the idea of even having additional fora in order to have some further technical discussions on those issues. One of them suggested was PQRI or a series of meetings, et cetera.

So, taking that into account, the next step would be to issue this document as a draft guidance not yet for implementation, then get the full public comment and then to issue a final guidance to the industry.

The time frame would be dependent upon those forums that we determined to get additional technical input. Obviously, we have been working on this since 1997 so the impetus is to do this on a quicker pace than we have before to get these issues fully aired and be able to go forward with the draft and the guidance process.

As you could see from the amount of scientific debate, and so forth, it does take a good bit of time but it is a process that we want to work on intently over the beginning part of next year.

DR. SHEK: Just maybe a general comment and some kind of a concern, and then maybe at least

a thought on the pass-forward. We started, I think, the meeting in the morning with a big boom. Being part of the industry, but seeing some of the matrix in the morning and to some aspect not being directly involved with a parenteral product, I would be scared as hell to go and buy a vial today and parenteral vials, looking at the 10- to 20-fold increase in sterility failures.

That goes out to the public domain. If that is really the case, then we have a big problem. But then, during the day, I think we found out that we really don't know what those numbers mean. Like any other matrix, if you don't define it, you are very dangerous playing with those numbers.

Looking at some of the numbers I have seen, it is one-third of those maybe the last three years had to do something which is not directly relevant to what we talked about today, whether it is alcohol swabs in a kit that were recalled or one issue with one company that something happened. I think it is important to exactly know where we stand, what are the issues.

Saying that, I want to just make sure that I am not being misunderstood. We, as an industry,

have to achieve to try to do the best. But, on the other thing, I think we shouldn't allow the public--I was listening here and there was quite a significant debate even of issues like sterility, can we combine terminal-sterilization with an aseptic process and ensure that the product at the end--had better assurance that it is sterile.

For example, if I sterilize my components and then I aseptically put them together and then, at the end, I am going to expose them to some kind of terminal sterilization, do I really add some assurance that it more sterile because if something in this process I introduce, some microorganism, and I cannot use full terminal sterilization? Did I really improve the process.

The reason I am bringing it up is maybe because the model of the PAT, and I don't know whether PQI--basically, we had one or two meetings in specific areas with specific experts trying to digest and find out what will be the best approach, on the long run, might be a faster way to go and get a good high-quality document.

DR. LEE: Judy, you are motioning to say something.

DR. BOEHLERT: Why not? I think it is

clear from the discussion today that the time has come to revise the 1987 document. There is nobody that disagrees with that. I also think it was clear from what I heard in the discussion that this document that has been put out is a good place to start.

It is not the end. There are clearly some technical issues that you need further discussion around media fills, on duration, on the number of units, around environmental monitoring, around isolator technology, a number of issues.

Rick, I think industry appreciates all the latitude words you put in there, but those latitude words, as somebody pointed out, need to be meaningful to investigators and to industry. They shouldn't be put there so we have a good defense when we get cited, but they should be put there to help the investigator to understand that other approaches are viable and are accepted.

We are not looking for good defenses. We are looking for a process that we can put in place and defend without getting a 483. So I fully support continuing dialogue on these issues. I think putting it out for general comment now is a very good thing to do. I think we are at that

point.

It is not without issues. It is not without things that need to be discussed. At least we know what those are, I think, from today's meeting.

DR. LEE: Anybody else wish to make a comment? Joe, have you heard enough?

MR. FAMULARE: I don't know if that is the best way to put it, Dr. Lee.

DR. LEE: Do you have sufficient guidance?

MR. FAMULARE: That's right. I think the meeting today was an excellent forum for discussing this document. We made the decision to bring the concept paper forward that we have been working on for such a long period of time to bring it into this discussion rather than to come here and start with a blank piece of paper.

I think that really invigorated the discussion and helped us to cover the various points by having this paper out there. We heard some very good discussions about the scope of the document in terms of certain examples were pointed out, certain things should be added to the document.

One example was clean-in-place,

steam-in-place. We also heard that maybe certain things should not be added to the document. We heard some call for using certain terminology that is more modern and iso-based. We heard for the call for harmonization wherever possible or to, at least, put an interpretation table in to explain our terminology against, for example, European terminology.

We had, not necessarily along those lines, but we had mentioned, for example, that in the European Union, they look as a first principle to see whether the product can withstand terminal sterilization as a first principle in going forward and deciding the process.

We, in this guidance document, are just looking at that also as a first principle and we are not trying to mandate that that is the way every process be set in this guidance document but, again, to at least look at the scientific value of that aspect.

We have certainly had a lot of discussion today about the level of specificity of the document. If you remember this morning, we discussed about meeting the goals of the current agency program concerning the GMPs for the 21st

Century, having a risk-based critical-control-point-based and a program that will encourage innovation.

So, while we put in the types of things that we hoped would encourage innovation, once we get to those things, such as isolated barriers, well then the natural question is, what is your expectation for that innovation. Certainly, we have heard a lot of debate around that.

So, again, we want to try to strike the proper balance in the document whether we look at various backgrounds or sterilization levels, that we are not being so prescriptive to discourage the use of what everyone would agree would be more modern technology for higher quality but, again, to give some comfort level to the industry as to what they are shooting for in putting in place that type of technology. As they bring it on new, there is a comfort level that is being sought.

There was, as was just discussed, discussion about what additional process is needed to further develop the document in terms of this committee. There was discussion of PQRI and discussion of any sort of series of meetings. We will look at those very intently to fully flesh out

all the debates and the good discussions that were brought up in the various areas that were brought out today.

Again, we basically focussed on five major areas today in looking at the document as a whole; design and control, the sterilization options, personnel, environmental monitoring and media fill. So we will look in those general areas again to see where we could further enhance the discussion so that we could put forward the best work product.

The main thing to realize is that we will take all this input as we go forward in developing what will be our draft guidance for public comment. It was very good to have this forum to get the full input of academia, industry and the advisory committee and our special guests here today in putting forward the document.

The best thing that I would want to acknowledge is to thank my colleagues in OPS for allowing this forum now to go forward to discuss traditional GMP-type documents. It is, I think, a good segue into what we are looking on moving forward in terms of the Subcommittee on Manufacturing and the discussion as Ajaz led it off today, and having a very technical and

controversial issue such as this being discussed today I think is a good lead into the whole topic in the advisory committee and sets the stage for future successful discussions and a wide variety of issues.

With that, I will ask my colleagues from ORA and from CBER if they have anything to add. I will go to CBER first.

MR. ELTERMAN: Thank you, Joe. I don't have many specifics to add although I do appreciate the comments that we received on the document today. It is interesting that a lot of discussions parallel the discussions that we had internally to get it this far. So we faced a lot of those same issues and what you see is sort of the compromise of the thought process in terms of the specificity, in terms of the level of detail.

The one particular plug I would like to make would be for the last appendix. We didn't have any discussion on the aseptic processing for bulk as it applies to some of the biological products. That was sort of an addition that we had to add to the document above and beyond the 1987 document because that was something that we felt was needed.

A lot of our products are processed aseptically from start to finish. So, to the extent that we could begin to address those issues, we thought it was important to include it in an overall document that addressed aseptic processing as opposed to having a separate guidance document.

So if you have particular comments on that, we would certainly be willing to hear them to beef up that section.

MR. ELLSWORTH: I don't have very much to add. I join with industry. I think it is time that we have a good, solid, science-based guidance document on this both for the industry and for the investigators that have to often do the inspections.

I guess, from my perspective, I think I have seen a couple of areas that were identified. I think it is very helpful--areas where I think there can be more scientific input. I am not sure if I have got it all catalogued. I see the area of media fills and environmental controls as being two major areas that we probably could use more scientific input on.

I would hope that we can find the proper forums to get that input from the experts that are

in the industry and the consultant side as well as the Agency. Maybe PQRI or some other forums might be forums we can get stronger scientific input.

We are not going to get all the answers, I think, but maybe if we can reach some consensus on the best way to go using that expertise.

DR. HUSSAIN: From an OPS side, I think this was a demonstration of how we can work as a team. I think we have tried to achieve that. So I think, for the manufacturer subcommittee and, I think, the next steps we will taking, the team approach has to work and I am pleased that I think it is working.

DR. LEE: To go back to the theme of this meeting, cGMP in the 21st Century. The challenge is always to think differently and I think this is a good example of making the process transparent and making everybody feel the ownership of the product that ultimately will come forward.

On that note, should I turn it over to Helen? I think she is going to say a few remarks.

Conclusions and Summary Remarks

MS. WINKLE: I appreciate the opportunity to have a few closing remarks. I will make them quick because I know you all are anxious to get out

of here. I don't want you to pull the plug on me.

DR. LEE: Not yet. I always have to have the meeting end on time.

MS. WINKLE: I just want to go over the last two days and sort of talk a little bit about what we accomplished and then I have a few other remarks to make as well.

Yesterday's meeting was basically devoted to getting reports from the two subcommittees, the NCSS and the PAT. I really appreciate the work that has gone into especially the NCSS. I appreciate Dr. Doull's work with that subcommittee and I appreciate the tolerance of this advisory committee and that subcommittee as we made some decisions on how best to handle pharm-tox issues in the Center.

I think the idea of moving the NCSS to NCTR and developing the pharm-tox subcommittee under the auspices of this advisory committee will really help us in making scientific decisions in this area in the past. I think that the decision is actually a very good one.

As far as the PAT Subcommittee, I think tomorrow's meeting will help us make some decisions as to where we are going from here. We still have

a lot of issues we need to discuss. I want to thank Ajaz. He has been very, very helpful in working with that subcommittee and helping us focus on the variety of issues that are involved in making some decisions on where we are going with PAT.

Also, I want to thank Dr. Layloff who served as the chair of that subcommittee. Again, I think we are looking at moving this subcommittee into the Manufacturing Subcommittee but tomorrow, I think, will sort of tell how we are going to handle this in the future.

I also, though, want to thank the advisory committee. As I said yesterday, I don't think we could have moved ahead with PAT either from the subcommittee standpoint or from what we are doing internally with OPS if we didn't have the help of the advisory committee. So I really appreciate that.

Just to wrap up on the other things that were discussed yesterday, blend uniformity; I think this issue has come to a close. I think that the committee has given us enough input now that we can move ahead with the recommendations that were provided by PQRI and to go ahead and finalize a

guidance to put out in draft on the subject of blend uniformity.

Again, your comments and recommendations have been invaluable in helping us get there. I know you are probably tired of talking about it since I think we have brought it up in three different meetings, but I really appreciate your input.

The CMC Risk Reduction Project Burden Project, I appreciate the comments on this. Yesterday was just mainly an update on where we are but I want to tell you I am sensitive to the comments that were made here at the committee and also off-line by several of the committee members that we really needed to ensure that that initiative was coordinated closely with other initiatives including PAT. So we will certainly keep that in mind as we move ahead.

I, unfortunately, was trying to get across the Cabin John Bridge this morning when Ajaz brought up the topic of the Manufacturing Subcommittee. Although I missed the discussion, I do understand that it was very helpful in providing input from the advisory committee on where we needed to move with this subcommittee and, based on

your recommendations, we will start putting a membership together and start formulating that subcommittee.

I can't add much to what Joe and others have said today about the aseptic processing. I do appreciate the Office of Compliance coming in with their issue. I think it was an excellent discussion and, as Ajaz says, a very good way for us to work together as a team, the advisory committee, the Office of Compliance and OPS, in laying some of the scientific foundations for our decision making.

So I really think today's discussion was a success. I really appreciate the number of people who have helped discuss this subject. I know we had to bring in a lot of experts in this area and, again, I really appreciate your time.

I think the discussion today will help all of us in thinking through where we need to go from here.

Lastly, I want to just talk a little bit about all of the work that went into this meeting. Yesterday, Vince made several comments on his observations as far as his time on the advisory committee and what he has gotten from it. Part of

what he said was that the presentations were very, very good. I want to second that. I really appreciate the people who have taken their time to present to the advisory committee.

A lot of work goes into these presentations to help the committee understand but also to help us at FDA have a better understanding of the scientific issues that we need to address.

I, personally, wanted to recognize Ajaz for this. He spends an awful lot of time preparing for these meetings and I think that his dedication to ensuring that there is a strong science underpinning to the regulatory decision process shows through when you hear these presentations. So I personally want to thank him for that.

Vince, it has really been a pleasure to work with you. I can't tell you--we have really enjoyed it. You said yesterday that you have been probably one of the shortest-time chairs ever. You may be a short-timer, but, for me, you have been a long-timer. You have actually done three of my four advisory committees so, to me, you are the chair of the advisory committee.

It is always wonderful to talk to you. You always have very good input. I have learned a

lot, as I said, yesterday and I think everyone on the committee has learned a lot. I especially like the way you keep the committee moving. It has been very, very helpful, even though you have had to pull the plug several times on the microphone so that we will stop talking.

But you have really, really been a big benefit to the committee as we have moved ahead. In order to thank you and recognize you for the efforts that you have put in, I have a plaque of recognition. You probably don't want to take this on the plane.

DR. LEE: I don't want to take this with me.

MS. WINKLE: So I will just hold it up and we will ship it to you. This is recognizing Vince for being the chair of the Pharmaceutical Science Advisory Committee for the last three meetings, actually, 2001 and 2002. So, Vince, we really appreciate that. Thank you.

[Applause.]

DR. LEE: Thank you very much. Actually, this is teamwork. I could not have done it, as you know--everybody on the committee got here not because of me. I think they are here because of

their own stature. But I enjoyed the spirit of teamwork, the committee feelings, and also I would like to thank you for the opportunity to serve this committee. I think I have learned a great deal. In fact, I learned more and now I can go back and teach aseptic fill.

MS. WINKLE: I don't know that you will get to escape us completely.

DR. LEE: Anyway, I enjoyed the people around here and you know where I am, that I come to this time more often than I am in Los Angeles. Truly, I would like to thank all my colleagues on the committee, that they are fine people. I think that is a good part of it, the chemistry that we discuss openly. I think that we are not afraid to challenge the system, like Art tried to propose a new mechanism to--

MS. WINKLE: That is actually a good lead-in to my next remark. Although, Vince, I think you are a really hard act to follow, we thought long and hard and decided that Art was a good person to follow. So we have asked Dr. Kibbe if he would chair the committee for the next two years.

He has willingly agreed. Ajaz and I met

with Art a couple of weeks ago. We had a long discussion with him over dinner and he made a number of useful recommendations for helping us work toward enhancing the committee. I think, along with the recommendations, Vince, that you have already made, I think we are making a lot of progress with this committee. I agree it has been a very collegial group, very easy to work with and I appreciate everyone's involvement and I look forward to working with Art.

I also want to recognize the other people that are leaving the committee. Again, it has really been a great opportunity to work with some really fine scientists. I think that your contributions to science in the Agency has been invaluable and I want to thank all of you.

Many of you, as I said yesterday, I hope to see in other capacities, maybe working on the subcommittees, on some of those, or in other aspects of some of the working groups we may put together. So I do look forward to seeing each of you, but I do want to recognize those people that are leaving the committee.

This includes Dr. Jusko who will be on our Subcommittee for Clinical Pharmacology, Dr. Doull

who has also said he will help with the new Pharm Tox Subcommittee; Judy Boehlert, who will be working with us on the Manufacturing Subcommittee; Dr. Anderson, who has been invaluable as the consumer rep. We really appreciate it; last, Mary Berg, who isn't here today.

So, again, thank you. Thank you for your contributions and thank you for the last two days. They go quickly, don't they?

DR. LEE: They certainly did, especially with the good discussion. Helen, we would have gotten something for you, but you know that we could not do so.

MS. WINKLE: Thanks for the thought.

DR. LEE: On that note, a motion for adjournment?

[Moved and seconded.]

DR. LEE: The meeting is adjourned. Thank you very much.

[Whereupon, at 4:50 p.m., the meeting was adjourned.]

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